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Attenuation of Endothelium-mediated Vasodilation by Halothane

Sheila M. Muldoon, M.D., Jayne L. Hart, Ph.D.,† Kimberly A. Bowen, M.S.,‡ William Freas, Ph.D.§*

To determine whether halothane alters endothelium-mediated vasodilation of vascular smooth muscle, isolated ring preparations of rabbit aorta and canine femoral and carotid arteries were suspended for isometric tension recordings in Krebs-Ringer bicarbonate solution at 37° C. Acetylcholine and bradykinin have been shown to relax these norepinephrine contracted arteries *via* an endothelium-dependent process. In this study, these relaxations were reversibly and significantly attenuated by 2% halothane. However, halothane did not affect relaxations caused by nitroglycerin, which, in these vessels, acts by an endothelium independent mechanism. These results suggest that halothane is not interfering with cyclic guanylate-monophosphate mediated relaxation of vascular smooth muscle, but may interfere with the synthesis, release, or transport of the endothelium-derived relaxing factor. In addition, during contractions evoked by norepinephrine, halothane caused significant decreases in tension in both the canine carotid and rabbit aortic preparations, but increased tension in the femoral artery rings. These effects were not altered by mechanical removal of the endothelium. These results suggest a direct action of halothane on the vascular smooth muscle, which can result in either an increase or decrease in tension, depending on the specific vessel. In addition to its direct vascular effect, this study suggests a new action of halothane; it interferes with endothelium-derived relaxing factor-mediated relaxation of vascular smooth muscle. This action may contribute in part to the vascular alterations seen clinically during administration of halothane. (Key words: Acetylcholine. Anesthetics, volatile: halothane. Artery: aorta; carotid; femoral. Bradykinin. Endothelium: endothelium-derived relaxing factor. Norepinephrine.)

THE LINING OF BLOOD VESSELS consists of a layer of endothelial cells in direct contact with blood. It is now well established that this endothelial layer modulates vascular smooth muscle activity.[1] This modulatory function is accomplished through several mechanisms, including the release of constrictor and dilator mediators in response to vasoactive stimuli.[2] Although the original observation was made with acetylcholine (ACh),[3] it is now known that several substances including bradykinin,[4] ionophore A23187,[2,5] and substance P[2] also require the presence of endothelium to relax vascular smooth muscle. Pharmacological studies indicate that these vasodilators interact with the endothelial cells, triggering the entry of calcium and setting in motion the production and release of a substance called the endothelium-derived relaxing factor (EDRF).[2] This factor in turn activates the production of cyclic guanylate monophosphate (cGMP) in vascular smooth muscle which inhibits the contractile process and leads to relaxation.[2]

Halothane has been reported to cause vasodilation, an effect attributed to a direct relaxing action on vascular smooth muscle,[6] a reduction of sympathetic output, or a reduction in the effectiveness of physiologic stimuli on vascular smooth muscle.[7-9] The possible interactions of halothane with endothelial mechanisms have not been previously investigated, although Blaise *et al.* have reported an endothelium-dependent action of isoflurane on canine coronary arteries.[10] Because of the importance of the endothelium in controlling vascular tone, the present study was designed to investigate whether halothane influences endothelium-mediated vasodilation of vascular smooth muscle.

Materials and Methods

Male New Zealand rabbits (3–4 kg) and mongrel dogs (15–25 kg) of either sex were anesthetized with sodium pentobarbital (40 and 30 mg/kg iv, respectively). Rabbit thoracic aortae and dog carotid and femoral arteries were obtained and placed in cold Krebs-Ringer bicarbonate solution of the following composition (millimolar): 118.2 NaCl, 4.7 KCl, 2.5 $CaCl_2$, 1.2 $MgSO_4$, 1.2 KH_2PO_4, 25.0 $NaHCO_3$, and 5.6 glucose (pH 7.4). The vessels were cleaned of extraneous tissue and cut into rings (3–4 mm). The endothelium was carefully removed from some rings by rotating the vessels around a small metal blade.[3] Rings with and without endothelium were prepared from adjacent segments of the same vessel.

ISOMETRIC TENSION RECORDINGS

The rings were placed in 25-ml water jacketed organ baths (37° C) and equilibrated for 60 min in Krebs-Ringer solution continuously aerated with 95% O_2-5% CO_2. The Krebs-Ringer solution was changed at 15-min intervals during equilibration. During this time, the rings were stretched to a final optimal tension of approximately 10 g, determined by preliminary length-tension studies. The average optimal tensions used for the rabbit aorta and dog carotid and femoral arteries

* Professor of Anesthesiology, USUHS.
† Professor of Biology, George Mason University.
‡ Research Physiologist, USUHS.
§ Research Assistant Professor of Anesthesiology, USUHS.

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Address reprints requests to Dr. Muldoon: Department of Anesthesiology, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, Maryland 20814.

were 10.6 ± 0.2 g, 9.3 ± 0.2 g, and 9.2 ± 0.3 g, respectively. Tension development was measured with a Grass FT03 isometric force transducer attached to a recorder (Gould Brush, Model 2400, Quincy, MA).

Isolated blood vessels, in experiments similar to these, have been shown to exhibit little or no active tension.[11] Therefore, to study smooth muscle relaxation, tension first needs to be induced with a vasoconstrictor. Relaxation responses to ACh, bradykinin, and nitroglycerin were determined in rings contracted to a stable plateau tension by the addition of norepinephrine (NE) at concentrations that elicited approximately 60% of the maximum tension that develops in response to NE (ED_{60}). Furchgott has reported that this level of submaximal developed tension is optimal for studying ACh-induced relaxations.[5] A range of ACh and bradykinin concentrations was used to cause relaxations of 25, 50, and 70%, so that possible concentration-related interactions of halothane with EDRF could be assessed. ACh concentrations used for the rabbit aorta, dog carotid, and dog femoral arteries were: 1, 6, and 10 $\times 10^{-7}$ M; 1, 2, and 4 $\times 10^{-8}$ M, and 3, 10, and 30 $\times 10^{-8}$ M, respectively. The three bradykinin concentrations used (for dog carotid) were 3, 20, and 200 $\times 10^{-9}$ M. The nitroglycerin concentrations used (for dog carotid) were 5 and 10 $\times 10^{-7}$ M. Relaxations were expressed as per cent depression of the NE-induced developed tension. The vasoactive substances were removed from the organ baths by repeated washings with fresh Krebs-Ringer solution until a stable baseline was re-established. At least 25 min elapsed between successive exposures to NE.

Two experimental protocols were performed. The first examined the effects of 2% halothane on NE-contracted canine carotid and femoral arteries with and without endothelium. (Adequacy of endothelium removal was determined prior to the experiment by an absence of a relaxation response with ACh). Vessels with and without endothelium were contracted with the appropriate concentration of NE and, when the contraction had reached a plateau, or when changes in tension had stabilized (pretreatment tension), 2% halothane was added to the gas mixture for 10 min. Isometric tension was continuously monitored throughout the experiment and, following termination of the halothane treatment, the rings were aerated with a mixture of 95% O_2-5% CO_2 for 10 min prior to washing NE from the bath.

The second experimental protocol examined the effect of halothane on the ACh or bradykinin-induced release of EDRF from endothelial cells of dog carotid and femoral arteries and rabbit aortic rings. This protocol consisted of a pre-treatment period during which the effect of the vasodilators was determined on NE-contracted rings, followed by an experimental period in which the effect of halothane on this relaxation was examined, and a final post-treatment relaxation period performed in the absence of halothane. These experimental periods were separated by at least 25 min, during which time the rings were washed at 5-min intervals. Simultaneous time controls were run for all experiments in which vascular rings were treated in an identical manner, but without exposure to halothane. Dog carotid artery rings were also used to study the effect of halothane on endothelium-independent vascular relaxations following addition of nitroglycerin using the previously described experimental design.

Drugs

The drugs used were acetylcholine chloride (Sigma, St. Louis, MO), l-norepinephrine HCl (Regis, Morton Grove, IL), bradykinin (Sigma), nitroglycerin (ICI Americas, Inc., Wilmington, DE), and halothane (Halocarbon Laboratories, Hackensack, NJ). Stock solutions were prepared daily in distilled water and kept on ice during the experiment. The drugs were added to the bath in volumes of 100 μl or less. Halothane was delivered from a calibrated vaporizer to give concentrations of 2% in the O_2-CO_2 mixture aerating the Krebs-Ringer solution. The concentration in the resulting gas mixture was monitored by an infrared halothane analyzer (Sensor Medics, Model LB-2, Anaheim, CA), which was calibrated daily using a standard halothane calibration gas mixture (Scott Medical Products, Plumsteadville, PA). Concentrations of halothane in Krebs-Ringer solution were measured by a gas chromatographic method previously described.[8] For 2% halothane, the bath concentration was 9.92 ± 0.89 mg/100 ml (n = 10). For some experiments, halothane was redistilled in glass at 49–50° C to separate it from the antioxidant, thymol.

Statistical Analysis

Each experimental group consisted of vascular preparations taken from five to seven different dogs and aortae taken from four different rabbits. The data are shown as mean ± SEM. The data were analyzed by multivariate analysis of variance. Differences were considered significant at $P < 0.05$.

Results

Effect of Halothane on Norepinephrine-Contracted Vascular Preparations

Femoral Artery: The response of the canine femoral artery to NE was characterized by development of an initial peak tension followed by a gradual decrease which we have designated pretreatment tension. The ED_{60} for NE (3×10^{-6} M) produced similar contractile

responses in vessels with endothelium (12.5 ± 0.4 g peak and 10.6 ± 0.3 g pretreatment tension), and without endothelium (14.4 ± 1.2 g peak and 12.0 ± 1.5 g pretreatment tension). Halothane (2%), added to the aerating mixture when the contractile response of these vessels had stabilized, caused a significant increase in tension. These increases averaged 2.1 ± 0.6 g and 2.3 ± 0.6 g for vessels with and without endothelium, respectively, and were not significantly different from each other (fig. 1). The effect of halothane was reversible.

Carotid Artery: The ED_{60} for NE (1×10^{-6} M) produced similar contractile responses in canine carotid artery rings with (8.3 ± 0.2 g) and without (7.5 ± 0.8 g, n = 5) endothelium. Halothane (2%), added to the aerating mixture when the contractile response of these vessels had stabilized, caused a significant decrease in tension which averaged 1.5 ± 0.4 g and 1.4 ± 0.2 g for vessels with and without endothelium, respectively (fig. 2). This effect was also reversible when halothane was discontinued.

NE Contractions and EDRF-Mediated Relaxations in the Presence and Absence of Halothane

This protocol required sequential administration of ED_{60} concentrations of NE to paired canine femoral and carotid vessels with endothelium intact. Three sequential administrations of NE did not alter tension development with time in either vessel. At the plateau of NE contraction, increasing concentrations of ACh caused dose-related relaxations in all vessels. One ring of each pair received halothane for 10 min prior to and during the second NE-induced contraction, while the other ring was not exposed to halothane.

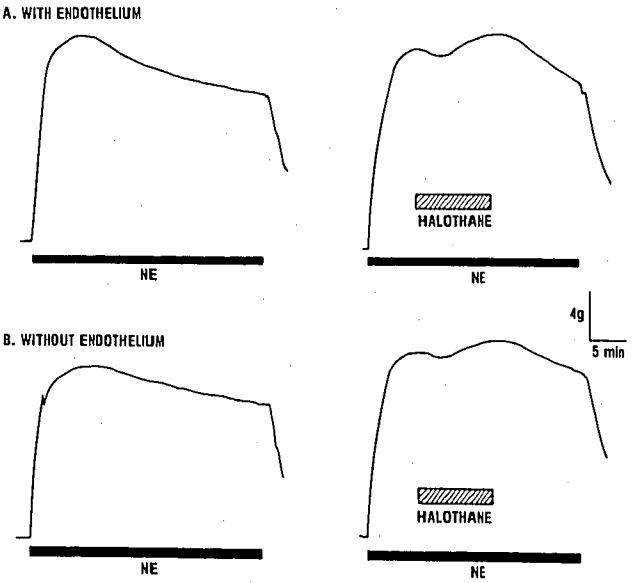

FIG. 1. Isometric tension recording of canine femoral artery rings contracted with NE (3×10^{-6} M), with the endothelium intact (*A*), and with the endothelium removed (*B*). In both, the NE contraction was characterized by the development of an initial peak tension followed by a gradual decrease over a 20-min period (tracings on the left). Halothane (2%, 10 min; hatched bar) added at the plateau of the NE contraction for 10 min caused a significant increase in tension in vessels with and without endothelium (tracings on the right). NE contraction was terminated by washing with fresh Krebs-Ringer solution.

Representative tracings of the effect of halothane on this ACh-induced relaxation of the femoral artery and a simultaneously run time control are shown in figure 3. In the NE-contracted femoral artery, prior to exposure to halothane, increasing concentrations of ACh (3, 10, and 30×10^{-8} M) produced relaxations of 2.9 ± 0.5, 5.6 ± 1.0, and 7.4 ± 1.5 g. Halothane (2%) significantly decreased these relaxations (table 1). These effects were

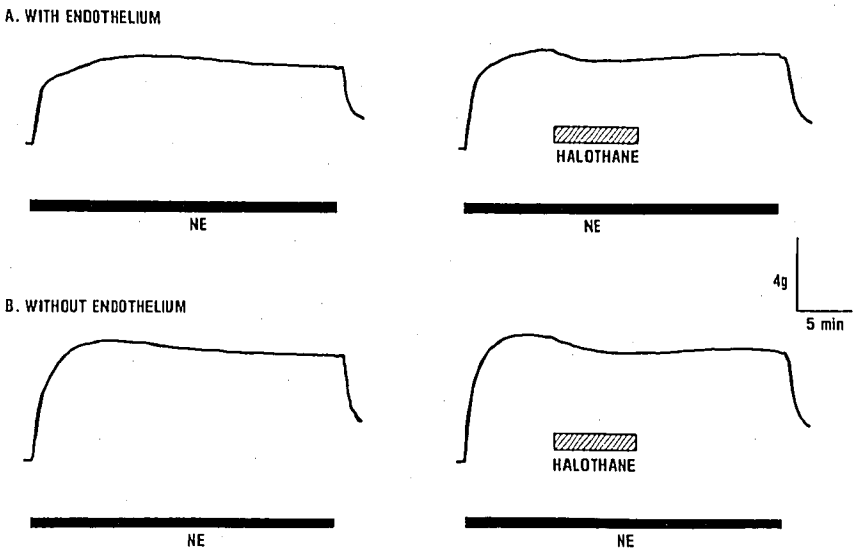

FIG. 2. Isometric tension recording of carotid artery rings contracted with NE (1×10^{-6} M), with the endothelium intact (*A*), and with the endothelium removed (*B*). In both, the NE contraction was characterized by the development of a initial peak tension followed by a gradual decrease over a 20-min period (tracings on the left). Halothane (2%, 10 min; hatched bar) added at the plateau of the NE contraction for 10 min caused a significant decrease in tension in vessels with and without endothelium (tracings on the right). NE contraction was terminated by washing with fresh Krebs-Ringer solution.

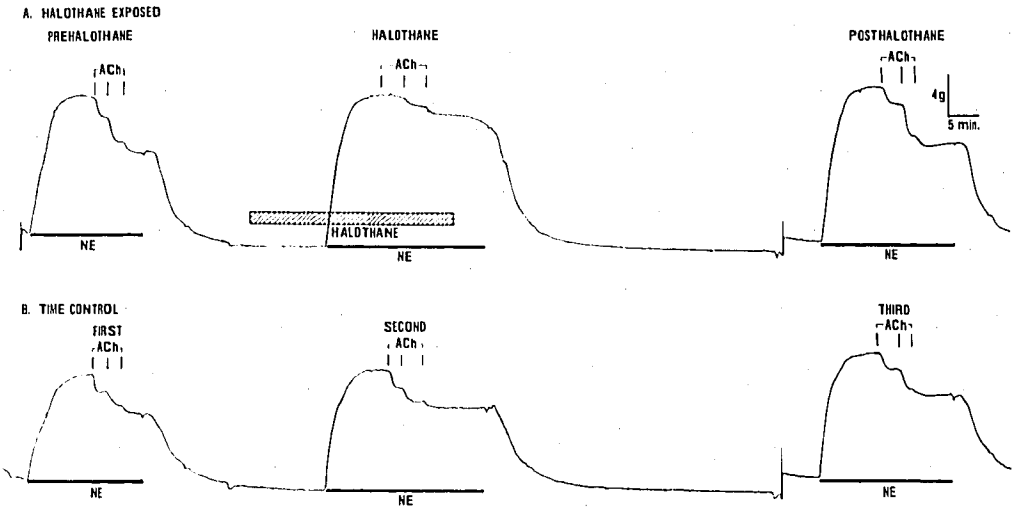

FIG. 3. Representative isometric tension recording of the effect of halothane on ACh-induced relaxations in NE-contracted femoral artery rings. After a stable response to NE-induced contraction occurred, the vessel was relaxed with increasing concentrations of ACh (3, 10, and 30 × 10^{-8} M). Prior to and during the second contraction/relaxation process, vessel (*A*) was exposed to halothane (2%). Tracing (*B*) shows the results of ACh relaxations in simultaneously run time control vessels not exposed to halothane.

significant at all ACh concentrations. In contrast, sequential ACh relaxations of the simultaneously run time control preparations were not significantly different from one another (table 1).

In canine carotid arteries contracted with an ED_{60} concentration of NE, increasing concentrations of ACh (1, 2, and 4 × 10^{-8} M) produced relaxations of 0.7 ± 0.2, 1.6 ± 0.4, and 2.6 ± 0.6 g. Halothane significantly attenuated the ACh-induced relaxations (fig. 4A). The results were similar using either redistilled, thymol free, or the standard commercial preparation of halothane. Successive ACh-induced relaxations did not change significantly with time in the control vessels (fig. 4B).

In order to determine the effect of halothane on ACh-induced relaxations of vessels from another species, paired rings of rabbit aorta were contracted with an ED_{60} concentration of NE. ACh (1, 6, and 10 × 10^{-7} M) caused dose-related relaxations (1.2 ± 0.2, 2.6 ± 0.4, and 3.5 ± 0.6 g). Halothane significantly attenuated the ACh-induced relaxations as compared to the simultaneously run time controls (fig. 5).

Bradykinin-induced relaxations of NE-contracted canine carotid arteries were examined. The protocol used was similar to that previously utilized for ACh-induced relaxations. Increasing concentrations of bradykinin (3, 20, and 200 × 10^{-9} M) produced relaxations of NE-contracted rings of 0.9 ± 0.2, 1.9 ± 0.3, and 3.2 ± 0.5 g. Halothane (2%) significantly attenuated these responses (fig. 6). There was no significant change in the bradykinin-induced relaxations for the time control vessels.

TABLE 1. Effect of 2% Halothane on Acetylcholine-induced Relaxations of the Canine Femoral Artery

Acetylcholine Concentration (×10^{-8}M)	Prehalothane (% Decrease)	Halothane (% Decrease)	Posthalothane (% Decrease)
Halothane exposed arteries			
3	25 ± 5	8 ± 4*†	19 ± 8
10	45 ± 6	17 ± 7*†	38 ± 6
30	59 ± 9	26 ± 7*†	49 ± 9
Time control arteries			
3	18 ± 7	17 ± 6	15 ± 6
10	36 ± 3	33 ± 12	28 ± 5
30	47 ± 4	42 ± 6	39 ± 5

Tension developed with an ED_{60} of norepinephine averaged 13.6 ± 2.9 g for halothane exposed vessels and 11.3 ± 2.1 g for time control vessels. Relaxations with ACh are expressed as a percent decrease of the NE contraction. Values are mean ± SEM. Femoral arteries were taken from five dogs and pairs of vessels, halothane-exposed and time control, were studied simultaneously.

* Significantly different from pre-halothane value.

† Significantly different from time control values obtained in simultaneously run time control arteries.

EFFECT OF HALOTHANE ON VASCULAR RELAXATIONS NOT MEDIATED BY EDRF

Nitroglycerin (5 and 10 × 10^{-7} M) causes vascular relaxations of NE-contracted canine carotid vessels by a mechanism independent of EDRF generation. Nitroglycerin-induced relaxations of NE-contracted vessels were dose-related (2.3 ± 0.4 and 4.7 ± 0.6 g), and halothane (2%) did not significantly alter these relaxations (table 2).

Discussion

The vascular effects of halothane have been the subject of a large number of previous studies, and the general consensus is that halothane causes vasodilation in specific vascular beds either by a direct depressant action on vascular smooth muscle[6] or by an indirect attenuation of vasoconstrictor activity.[7-9,11] This consensus was arrived at prior to recent studies establishing the

importance of endothelium-derived factors in modulating vascular smooth muscle activity. Therefore, it seemed appropriate to investigate the action of halothane on vessels in which EDRF is being generated. Our studies indicate that halothane decreases endothelium-mediated relaxation in canine and rabbit arteries, possibly by interfering with the production, the transit, or the action of EDRF on smooth muscle.

It is now well established that the major mechanism for relaxation of certain blood vessels by ACh, and a number of other vasoactive agents, is indirect, and requires the agent to first act on endothelial cells to stimulate the production and release of a relaxing factor.[1,2] When canine femoral or carotid arteries were stimulated by ACh to produce EDRF, endothelium-induced relaxations were significantly reduced by halothane. This action of halothane was not limited to canine vessels, but was also observed in rabbit aortic rings, indicating that this effect is not species specific.

The effect of ACh on endothelial cells is mediated *via* muscarinic receptors. Halothane has been reported to interfere with the muscarinic actions of ACh in sympathetic nerve endings[11] and in skeletal muscle.[12] To examine the specificity of this action of halothane on endothelial relaxations, we used a non-muscarinic substance, bradykinin, to induce EDRF relaxations. Halothane interfered with the endothelium-induced relaxations of ACh and bradykinin to a similar degree. Since the effect of bradykinin is endothelium-dependent, but is not mediated by muscarinic receptors, this effect of halothane is not specific to muscarinic receptor activation. It is possible that halothane acts at a site distal to the ACh and bradykinin receptors, or that it interferes with non-receptor-mediated generation of EDRF. However, since non-receptor-mediated agonists were not tested, conclusions about specific sites of action of halothane cannot be made from these studies.

Although our studies do not identify the mechanisms by which halothane attenuates the EDRF-mediated relaxation, the nitroglycerin results indicate that these concentrations of halothane are not interfering with cGMP-mediated relaxations of vascular smooth muscle. Both nitroglycerin and EDRF are reported to produce vascular relaxation by increasing the production of cGMP which inhibits the smooth muscle contractile

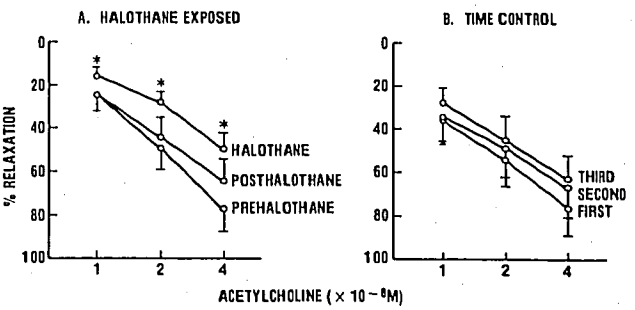

FIG. 4. *A*. Effect of halothane (2%) on ACh-induced relaxations of NE-contracted canine carotid artery preparations, and the simultaneously run time control vessels (*B*). Data were expressed as per cent relaxation of the NE contraction, mean ± SEM (n = 7). Tension development due to the addition of NE on halothane exposed and time control vessels averaged 3.4 ± 0.7 g and 2.9 ± 0.8 g, respectively. *Indicates that ACh-induced relaxations were significantly less in the presence of halothane than the pre- and post-halothane values. Relaxations with successive ACh concentrations were not significantly different from one another in the time control vessels.

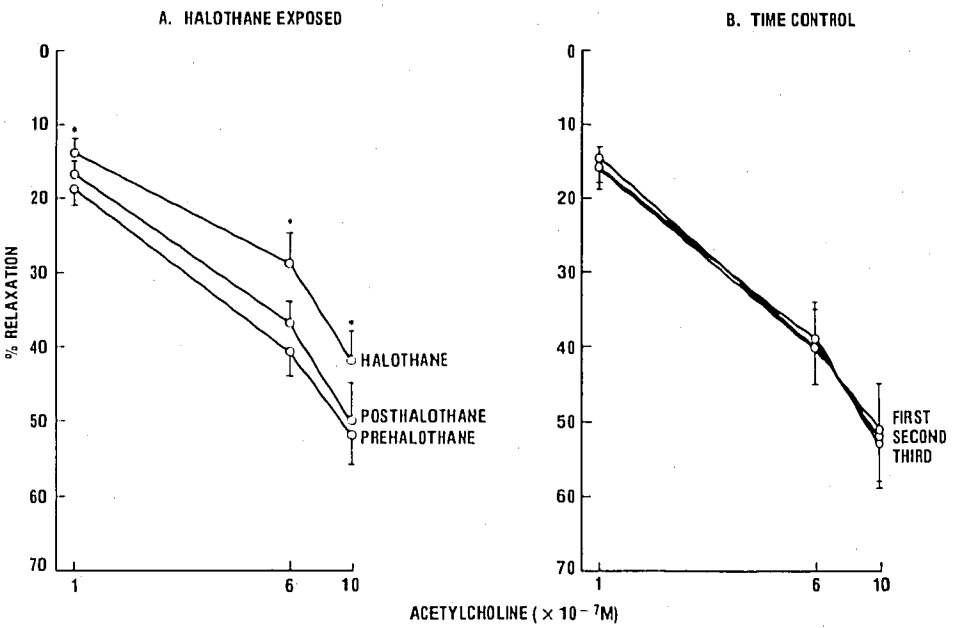

FIG. 5. *A*. Effect of halothane (2%) on ACh-induced relaxations in rabbit aortic rings, and the simultaneous time control vessels (*B*). Data were expressed as per cent relaxation of the NE-induced contraction, mean ± SEM (n = 4). Tension development on halothane-exposed and time control vessels averaged 6.7 ± 3.3 g and 6.7 ± 1.4 g, respectively. *Indicates that ACh relaxations were significantly less than pretreatment values. Relaxations with successive ACh concentrations were not significantly different from one another in the time control vessels.

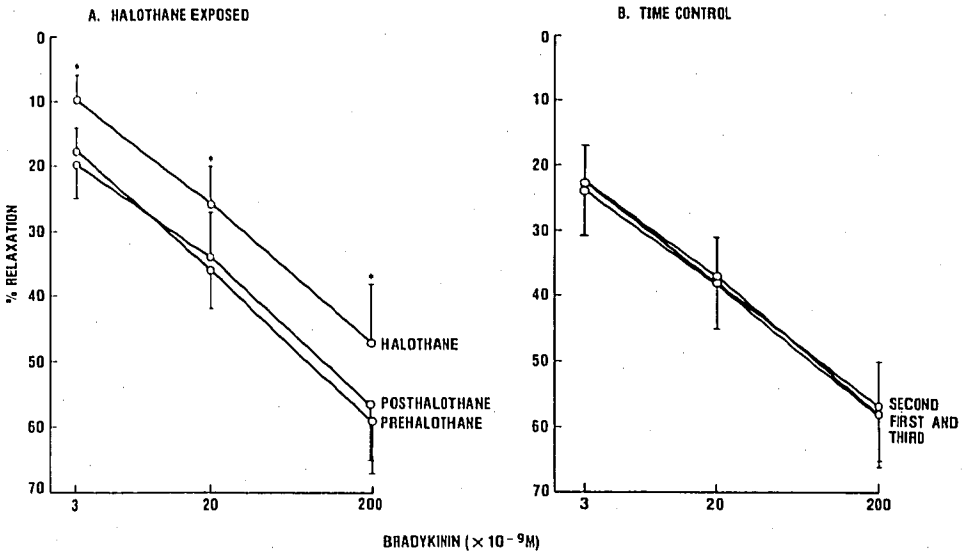

FIG. 6. *A.* Effect of halothane (2%) on bradykinin-induced relaxations of canine carotid artery rings, and the simultaneous time controls (*B*). Data were expressed as per cent relaxations of the NE-induced contraction, mean ± SEM (n = 6). Tension development on halothane-exposed and time control vessels averaged 5.8 ± 0.9 g and 4.6 ± 0.6 g, respectively. *Indicates that bradykinin-induced relaxations in the presence of halothane were significantly less than the prehalothane values. Relaxations with successive bradykinin applications were not significantly different from one another in the time control vessels.

process.[13] Since halothane only inhibits the action of acetylcholine and bradykinin, and not that of nitroglycerin, its action may be at some site(s) between the endothelial site of interaction and the smooth muscle production of cGMP.

An increase in intracellular free calcium has been reported to be necessary for the release (production) of EDRF by the endothelium. Although the initial source of this calcium appears to be from intracellular sites, extracellular calcium plays a major role, especially during sustained release (production) of EDRF.[14,15] Halothane has been reported to interfere with cellular calcium dynamics in a number of different ways. In cardiac muscle,[16] and other tissues,[17] halothane decreases calcium influx across the plasmalemma. Thus, suppression of calcium entry into the endothelial cells may be a mechanism by which halothane interferes with EDRF-mediated relaxation.

TABLE 2. Effect of 2% Halothane on Nitroglycerin Relaxations in Canine Carotid Artery With and Without Endothelium

Nitroglycerin Concentration ($\times 10^{-7}$ M)	Prehalothane (% Decrease)	Halothane (% Decrease)	Posthalothane (% Decrease)
Arteries with endothelium			
5	35 ± 8	32 ± 7 n.s.	38 ± 8
10	67 ± 9	64 ± 8 n.s.	73 ± 7
Arteries without endothelium			
5	52 ± 9	53 ± 8 n.s.	58 ± 7
10	81 ± 8	80 ± 6 n.s.	87 ± 3

Tension developed with an ED_{60} of norepinephine averaged 7.2 ± 0.7 g for the arteries with endothelium and 6.9 ± 0.7 g for the arteries without endothelium. Relaxations with nitroglycerin are expressed as a percent decrease of the contraction. Values are mean ± SEM. Carotid arteries were taken from seven dogs and pairs of vessels with and without endothelium were studied simultaneously. n.s. = not significantly different from pre-halothane or post-halothane values.

Active generation of EDRF appeared to be necessary for the effects of halothane to be expressed, as endothelium removal did not influence the actions of halothane on canine femoral and carotid arteries that were not being stimulated by ACh to actively produce EDRF. There have been reports that *in vitro* preparations of vessels continuously produce small ("basal") amounts of EDRF and greater amounts when activated with ACh or other endothelium-dependent vasodilators.[2,15] *In vivo*, most vessels are continuously exposed to pressure and flow, and the amount of EDRF released has been shown to be directly related to flow and pressure.[2,18] ¶ Therefore, under physiological conditions in the intact circulation, it seems reasonable to predict that the depressant effects of halothane on EDRF-mediated vasodilation may be an important component of the net effects of halothane on the cardiovascular system.

The magnitude of the 2% halothane inhibition of the EDRF-induced relaxation varied between 20 and 68% in different vessels for various concentrations of ACh or bradykinin. Higher concentrations of halothane (3%) did not increase this inhibition (unreported data). Other conditions (anoxia) or substances (*i.e.*, quinacrine, methylene blue, and hydroquinone[1]) have been reported to cause complete inhibition of EDRF-mediated relaxation. Thus, halothane is not as effective an inhibitor as these agents.

Vanhoutte has stated that EDRF may be chemically inactivated by antioxidant substances or by superoxide

¶ Fridovich I, Hagen PO, Murray JJ: Endothelium-derived relaxing factor: In search of the endogenous nitroglycerin. News Physiol Sci 2:61–64, 1987

anions[2] during its transit from the endothelial cell to the smooth muscle. The antioxidant, thymol, is in commercial halothane solutions; however, it should not vaporize under the conditions of these experiments. Also, redistilled thymol-free halothane still caused inhibition of ACh relaxation in the carotid artery. Therefore, this preservative does not appear to be responsible for the observed halothane effects.

In addition to the interactions between halothane and EDRF, halothane increased tension of NE-contracted canine femoral vessels and decreased tension in NE-contracted canine carotid arteries and rabbit aortic rings. These effects were not dependent on, or influenced by, the endothelium, since they were unaltered by the removal of these cells. (The mechanisms of these changes in tension are unknown.) Vatner and Smith[19] also observed variable vascular responses to halothane. They reported that, in awake, chronically instrumented dogs and primates, halothane caused dilation in most vascular beds, but constriction in some. The type of response was dependent on concentration of the anesthetic, vascular bed, and duration of exposure to halothane. Our *in vitro* studies support these *in vivo* findings of regional heterogeneity of vascular responses to halothane, and indicate that the net effect depends on the sum of halothane activities at different sites. In summary, this study suggests a new action for halothane; it interferes with EDRF-mediated relaxations of vascular smooth muscle. This action may contribute in part to the vascular alterations seen clinically during administration of halothane.

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