Halothane, Enflurane, and Isoflurane Do Not Affect the Basal or Agonist-stimulated Activity of Partially Isolated Soluble and Particulate Guanylyl Cyclases of Rat Brain

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Background: Evidence suggests that inhalational anesthetics interact with the nitric oxide–guanylyl cyclase signaling pathway in the central nervous system and that the inhibition of this pathway in brain may result in an anesthetic, analgesic, or sedative effect. The mechanism of the effects of inhalational anesthetics on this signaling pathway is not clear. This study attempted to determine whether inhalational anesthetics directly affect soluble or particulate guanylyl cyclase activity in a partially isolated enzyme system.

Methods: The effects of halothane (0.44–4.4%), enflurane (1.34–6.7%), and isoflurane (0.6–5.0%) on basal or stimulated soluble or particulate guanylyl cyclase activity were examined. Soluble guanylyl cyclase was isolated from whole rat brain and was stimulated by sodium nitroprusside or nitric oxide. Particulate guanylyl cyclase was isolated from rat olfactory bulb and was stimulated by rat atrial natriuretic peptide (ANP).

Results: None of the three anesthetics affected the activity of basal or stimulated soluble or particulate guanylyl cyclase at the concentrations examined in the current experimental conditions.

Conclusions: These results suggest that halothane, enflurane, and isoflurane do not directly interact with soluble or particulate guanylyl cyclases of rat brain. (Key words: Anesthetics; volatile: enflurane; halothane; isoflurane. Brain: nitric oxide. Enzyme: guanylyl cyclase; particulate; soluble. Nucleotides: cyclic guanosine monophosphate. Pharmacology: atrial natriuretic peptide; sodium nitroprusside.)

ENDOTHELIUM-DERIVED relaxing factor (EDRF), first discovered as an important regulator of vascular tone, is structurally likely to be nitric oxide (NO) or a related nitrogen oxide–containing compound. In endothelium, EDRF/NO is synthesized from L-arginine by a constitutive enzyme referred to as NO synthase. EDRF/NO then diffuses to vascular smooth muscle to stimulate soluble guanylyl cyclase and increases cyclic guanosine monophosphate (cGMP), which in turn induces muscle relaxation. The NO–guanylyl cyclase system is now recognized to exist in various tissues, including the central nervous system, where it functions as a neural messenger system.

Suppression of NO-dependent vasodilation by various inhalational anesthetics has been demonstrated in the peripheral vasculature by several groups. In brain, inhalational anesthetics have been reported to inhibit NO synthase activity and to decrease the cGMP concentration in specific brain regions. In addition, it has been established that activation of N-methyl-D-aspartate receptors in brain increased neuronal cGMP content through stimulation of the NO–guanylyl cyclase pathway, and several studies have demonstrated that N-methyl-D-aspartate–mediated neurotransmission is altered by anesthetics. It is therefore conceivable that inhibition of the NO–guanylyl cyclase pathway may result in an anesthetic, analgesic, or sedative effect. Indeed, Johns et al. demonstrated that L-Nω-nitro arginine methyl ester, a specific inhibitor of NO synthases, reduced the minimum alveolar concentration (MAC) for halothane in a dose-dependent and reversible manner, although controversy exists. Also, several groups provided evidence that the NO pathway is involved in mechanical nociceptive responses and thermal hyperalgesia.

The mechanism of inhibition of the NO–guanylyl cyclase signaling pathway by inhalational anesthetics is not clear and has been controversial. Several studies...
have suggested that inhalational anesthetics may interfere with the synthesis, release, or transport of EDF/NO.20–22 and a recent study by Hart et al.7 suggested that the effects of halothane on the NO–guanylyl cyclase pathway may involve an interface with guanylyl cyclase activation, based on evidence that halothane attenuated the vasodilation induced by NO or nitroglycerin and the NO-stimulated cGMP increase in rat aortic rings. Similarly, Nakamura et al.8 reported that halothane inhibited the vasorelaxation induced by sodium nitroprusside (SNP) and the cGMP increase stimulated by NO or SNP in rat aortas. However, a study by Eskinder et al.23 suggested that halothane activated particulate guanylyl cyclase but not soluble guanylyl cyclase in canine middle cerebral vessels. In contrast, Blaise et al.24 demonstrated that halothane interferes neither with endothelial cell release of EDF/NO nor with the guanylyl cyclase, but seems to modify EDF/NO half-life or its activated oxidation–reduction form.

Therefore, the current study, by using partially isolated enzymes, was designed to investigate whether inhalational anesthetics directly influence the activity of basal or stimulated guanylyl cyclase of rat brain.

Materials and Methods

This research protocol was approved by the Research and Animal Welfare Committee of the University of Virginia.

Nitric Oxide Solution Preparation

NO solutions were freshly prepared immediately before use, under anaerobic conditions by the method of Rengasamy and Johns.25 2 ml deoxygenated 50 mm tris(hydroxymethyl)aminomethane (Tris)–HCl (pH = 7.4) contained in a 7-ml Vacutainer tube (Becton Dickinson, Rutherford, NJ) at room temperature was saturated with NO by bubbling 50 ml pure NO gas, which had passed through a column of KOH pellets. This produced an NO stock solution of 1 mm as determined by the chemiluminescence method as described previously.26 Serial dilutions were made from this stock solution by removing aliquots with gas-tight syringes. These aliquots were added to deoxygenated 50 mm Tris-HCl (pH = 7.4) solution.

Preparation of Soluble and Particulate Fractions of Rat Brain

Whole brain (including both cerebral and cerebellum) and olfactory bulb were removed from halothane anesthetized Sprague-Dawley rats (250–300 g) after extensive in situ perfusion with ice-cold heparinized normal saline (2,000 U/L saline, 80 ml/rat cardiac perfusion with right atrial transaction) to minimize residual hemoglobin. Whole brain and olfactory bulb were used as the source of soluble and particulate fraction of guanylyl cyclases, respectively, because whole brain is rich in soluble guanylyl cyclase27 and olfactory bulb contains high quantities of atrial natriuretic peptide (ANP)–sensitive particulate guanylyl cyclase,28 which can bind to ANP (1–28) when partially isolated.29 Brain and olfactory bulb were washed in three changes of ice-cold homogenization buffer containing 50 mm Tris-HCl (pH = 7.4), 250 mm sucrose, and 0.2 mm benzamidine. They were then homogenized in ice-cold homogenization buffer with three Polytron homogenizer bursts of 30 s. The homogenate was centrifuged at 1,000g for 10 min at 2°C. The pellet was discarded and the supernatant was then centrifuged again at 105,000g for 60 min at 4°C. The supernatant was harvested and used in the soluble guanylyl cyclase assay. The pellet was washed three times with homogenization buffer and then stored in this buffer at –80°C until it was used in particulate guanylyl cyclase measurements.30 Protein concentrations were measured by the Bio-Rad (Hercules, CA) protein assay method.31

Administration and Equilibration of Inhalational Anesthetics with Reaction Mixture Solution

The reaction mixture solution (250 μl) contained in a 7-ml scintillation glass vial without a cap was gassed with humidified carrier gas (95% O2, 5% CO2) in the presence or absence of inhalational anesthetics. Carrier gas was delivered at 3 l/min through or not through a halothane, etرف, or isofluorane vaporizer and subsequently passed through a warmed (37°C) humidification chamber. Gas entry into each glass vial was valve regulated and maintained at 50 ml/min. Because of the humidification of the gas, no significant evaporation of the reaction mixture solution occurred during the course of the experiment. Reaction mixture solution was equilibrated with anesthetics for 5 min before the addition of enzyme (in a 10-μl volume) to start the reaction. Preliminary experiments were designed to determine the time course of equilibration of anesthetics in the reaction mixture solution. The concentration of anesthetics in the solution was measured by using standard gas chromatography methods.2 The concentration of anesthetics in the carrier gas after

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passing through the vaporizer was also confirmed by the same methods.9

Guananyl Cyclase Activity Assay
The guananyl cyclase activity assay was performed as described previously.30,32 The reaction mixture solution was prepared in a final volume of 250 µl containing 50 mm Tris-HCl (pH 7.4), 1 mm isobutylmethylxanthine, 4 mm MnCl2, 0.5 mm adenosine triphosphate (disodium salt, grade I: from yeast), 1 mm guanosine triphosphate (sodium salt, type III), 15 mm creatine phosphate, and 100 µg creatine phosphokinase. The reaction mixture solution was gassed with carrier gas in the presence or absence of anesthetics for 5 min in a 37°C water bath before the addition of enzyme (15–25 µg protein in 10 µl volume) to initiate the reaction. Rat ANP(1–28) (in 10 µl) was added just before the addition of enzyme. NO or SNP stock solution (in 10 µl) was added immediately after the addition of enzyme to the reaction mixture. The reaction continued at 37°C with or without guananyl cyclase activating agents with continuous gassing by carrier gas in the presence or absence of inhalational anesthetics. The reaction was terminated 5 min later by adding 250 µl ice-cold 0.2 N HCl. cGMP concentrations were quantified by radioimmunoassay as previously described.41,45 Preliminary experiments were carried out to determine the time course of guananyl cyclase activity in the presence or absence of stimulators.

Data Analysis
Results are presented as mean ± standard error of the mean. Each data point represents a mean of 2–4 experiments with a n (number of repetitions) ≥ 6. Statistical analysis was performed by one-way analysis of variance with multiple-range testing (the Newman-Keuls test) when the effects of inhalational anesthetics on the basal or agonist-stimulated guananyl cyclase activity were evaluated. Comparisons of guananyl cyclase activity in the presence or absence of NO, SNP, or rat ANP(1–28) and comparisons of soluble guanylyl cyclase activity at each dose of NO in the presence and absence of anesthetics were made by paired t test. P < 0.05 was accepted as significant.

Chemicals and Drugs
Adenosine triphosphate, isobutylmethylxanthine, Tris-HCl, MnCl2, guanosine triphosphate, creatine phosphate, creatine phosphokinase, SNP, sucrose, and benzamidine were obtained from Sigma Chemical (St. Louis, MO). Rat ANP(1–28) was obtained from Peninsula Laboratories (Belmont, CA). Halothane was obtained from Halocarbon Laboratories (Hackensack, NJ), enflurane from Airclo (Madison, WI), and isoflurane from Ohmeda Caribe (Liberty Corner, NJ). NO gas was obtained from Liquid Carbonic (Chicago, IL) and 95% O2, 5% CO2 gas from Roberts Oxygen (Waynesboro, VA).

Results
Equilibration of Inhalation Anesthetics in the Reaction Mixture Solution
The concentrations of halothane, enflurane, and isoflurane in the reaction mixture solution reached a plateau by 4–5 min over the concentration range of inhalational anesthetics used in this study (fig. 1). The final concentrations reached in the solution were within 10.1 ± 8.0% of the predicted value, calculated as previously described.41,45 The concentrations of halothane, enflurane, and isoflurane in the carrier gas were confirmed by gas chromatography to be accurate to within −1.9 ± 4.7% of the concentrations delivered by the vaporizer.

Effects of Inhalational Anesthetics on Basal and Stimulated Soluble Guanylyl Cyclase Activity
cGMP concentrations produced by soluble guanylyl cyclase progressively increased to 5 min of incubation time; thereafter the cGMP contents in the reaction mixture solution were stable throughout 30 min incubation. The presence of 0.1 mm of SNP increased the cGMP content at each incubation time but did not alter the time course pattern (fig. 2A).
Soluble guanylyl cyclase activity was significantly stimulated after exposure to 0.1 mm SNP for 5 min. However 0.44–4.4% halothane, or 1.32–6.7% enflurane, or 0.6–5.0% isoflurane did not significantly affect either the basal or 0.1 mm SNP-stimulated guanylyl cyclase activity (fig. 3).
NO (10−9–10−6 M) produced a concentration-dependent increase of soluble guanylyl cyclase activity; this increase was not affected by 4.4% halothane, 6.7% enflurane, or 5.0% isoflurane (fig. 4). Moreover, the soluble guanylyl cyclase activity stimulated by 1 µM NO was not inhibited by 0.44–4.4% halothane, or 1.32–6.7% enflurane, or 0.6–5.0% isoflurane (fig. 5).
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Fig. 1. Time course of the equilibration of halothane (A), enflurane (B), and isoflurane (C) in the reaction mixture solution. For each anesthetic, the highest and the lowest concentrations used in this study are shown. n = 6.

Effects of Inhalational Anesthetics on Basal and Stimulated Particulate Guanylyl Cyclase Activity

The time course of cGMP production of particulate guanylyl cyclase in the presence or absence of 1 μM rat ANP\textsubscript{(1-28)}, an agonist of natriuretic peptide receptor A, \textsuperscript{13} progressively increased up to the incubation time of 30 min. One micromolar rat ANP\textsubscript{(1-28)} significantly increased the cGMP concentration in the reaction mixture solution after 5 min (A and B).

Both basal and 1 μM of rat ANP\textsubscript{(1-28)} stimulated guanylyl cyclase activity increased by 0.44-4.4% halothane, or 0.6-5.0% isoflurane. These results, the time course of particulate guanylyl cyclase activity in rat brain, is presented in Figs. 2 and 3.

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The effects of halothane (A), enflurane (B), and isoflurane (C) on basal and sodium nitroprusside (SNP)-stimulated rat brain soluble guanylyl cyclase activity (n = 12). *P < 0.05 compared with basal guanylyl cyclase activity. cGMP = cyclic guanosine monophosphate.

Increased the cGMP concentrations in the reaction mixture solution after 5 min of incubation time (figs. 2B and 6).

Both basal and 1 μM of rat ANP (1-28)-stimulated particulate guanylyl cyclase activity were not significantly affected by 0.44–4.4% halothane, or 1.32–6.7% enflurane, or 0.6–5.0% isoflurane (fig. 7). To confirm these results, the time course experiments investigating particulate guanylyl cyclase activity with or without 1 μM rat ANP (1-28) were performed in the presence or absence of 4.4% halothane. Halothane did not affect either basal or 1 μM rat ANP (1-28)-stimulated cGMP.

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formation produced by particulate guanylyl cyclase (fig. 6).

Discussion

EDRF/NO is now recognized as the transduction mechanism for the activation of soluble guanylyl cyclase. This NO–guanylyl cyclase pathway has been demonstrated in a wide variety of tissue types, including brain.\textsuperscript{2,3,5} The interaction between inhalational anesthetics and the NO–guanylyl cyclase signaling pathway has been dynamically studied and it is generally accepted that inhalational anesthetics inhibit the NO–guanylyl cyclase pathway, although the actual site of this inhibition has been highly controversial.\textsuperscript{7–10,20,21,30–35}

We used partially isolated guanylyl cyclases from rat brain to specifically address the question of whether inhalational anesthetics directly affect particulate or soluble guanylyl cyclase activity. The use of partially isolated enzymes in the current study allows us to clearly distinguish the activity of soluble guanylyl cyclase from that of particulate guanylyl cyclase and also to avoid many of the potentially complicating factors associated with cultured cells or intact freshly isolated cells because multiple factors inside cells, such as oxidation–reduction state and endogenous inhibitors, may affect guanylyl cyclase activity.\textsuperscript{60–64} We investigated the changes of both basal and agonist-stimulated guanylyl cyclase activity in the presence or absence of inhalational anesthetics. Wide-ranging concentrations of halothane, enflurane, and isoflurane did not stimulate or inhibit basal soluble or particulate guanylyl cyclase activity, suggesting that these anesthetics do not influence cGMP production of these two types of guanylyl cyclase concentrations of halothane, also did not affect the SNP-induced particulate guanylyl cyclase activity. There was significant interaction between guanylyl cyclase activity, produced by different batches of enzymes, and concentrations of guanylyl cyclase experiments.

Initial studies by several groups suggested that the site of anesthetics on the NO–guanylyl cyclase pathway may be at the synthesis of EDRF/NO and may not be at the guanylyl cyclase activation. The results were that acetycholinesterase, a vessel relaxant, which is dependent, was inhibited by guanylyl cyclase, which is caused by the diazenide, guanylyl cyclic, was not able to identify Hart and colleagues with that 2 MCG significant vessel relaxation (NO concentrations to 3 × 10\textsuperscript{-5} M) were not significantly increased relaxation of rat aorta, or the other, was unable to identify Hart. Furthermore, NO-stimulated constriction to 5 × 10\textsuperscript{-6} M was rammed by halothane. Halothane may affect the activity of NO. One study by Su and colleagues\textsuperscript{7} to support the hypothesis that halothane increased diazenide, rings relaxed by 10\textsuperscript{-6} M and Zhuang study there was decreased tension of these rings. The inhibitory effect of halothane stimulation by SNP. Also, the authors demonstrated that if rat aorta was reduced by SNP, but not lower or higher concentration, the increase in cGMP of SNP was inhibited by halothane.

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...activity, suggesting that these three inhalational anesthetics do not influence cGMP production through either of these two types of guanylyl cyclases. The same concentrations of halothane, enflurane, and isoflurane also did not affect the SNP- or NO-stimulated soluble guanylyl cyclase activity nor the rat ANP$_{1-28}$-stimulated particulate guanylyl cyclase activity. However, there was significant interassay variation of apparent guanylyl cyclase activity, probably the result of the use of different batches of enzyme preparation with different concentrations of guanylyl cyclase for the different experiments.

Initial studies by several groups using arterial rings suggested that the site of inhibition of inhalational anesthetics on the NO–guanylyl cyclase signaling pathway may be at the synthesis, release, or transport of EDRF/NO and may not be at the point of guanylyl cyclase activation. The results supporting this conclusion were that acetylcholine- and bradykinin-induced vessel relaxation, which is receptor mediated and NO dependent, was inhibited by inhalational anesthetics, whereas nitroglycerin- and SNP-induced relaxation, which is caused by the direct activation of soluble guanylyl cyclase, was not affected. However, recently Hart and colleagues demonstrated that halothane (2 MAC) significantly attenuated NO-induced vessel relaxation (NO concentrations to 1 μM) and low concentrations (to 3 × 10$^{-8}$ M) of nitroglycerin-induced relaxation of rat aortic rings. Isoflurane, on the other hand, was unable to inhibit NO-induced relaxation. Furthermore, NO-stimulated cGMP content (NO concentrations to 5 × 10$^{-6}$ M) was also significantly attenuated by halothane. These results suggest that halothane may affect the activation of guanylyl cyclase by NO. One study by Su and Zhang, which was cited by Hart et al. to support their suggestion, also showed that halothane increased the tension of rabbit intact aortic rings relaxed by 10$^{-7}$ m SNP, although in the Su and Zhang study there was no indication that the increased tension of these rings was attributable to the inhibitory effect of halothane on guanylyl cyclase activity stimulated by SNP. Also, a study by Nakamura and associates demonstrated that SNP-induced relaxation of rat aorta was reduced by halothane (only at 10$^{-8}$ M but not lower or higher concentrations of SNP) and that the increase in cGMP of aorta stimulated by NO or SNP was inhibited by halothane, although similar inhibitions did not occur using isoflurane or sevoflurane. These studies suggest that the interaction of NO and soluble guanylyl cyclase may be a site of inhibition of the NO–guanylyl cyclase signaling pathway by halothane but not by the other inhalational anesthetics.

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Footnotes:

† Muldown SM: Personal communication. 1994.

Concentration of Anesthetic (%)
studied. However, this suggestion was not supported by other recent studies, which are more consistent with the early studies by Muldoon et al. and Toda et al., which failed to show an effect of halothane on nitrovasodilator-induced vasodilation.

The intact artery ring may be too complicated to define and evaluate clearly the effects of inhalational anesthetics on specific sites of the NO–guanylyl cyclase signaling pathway because, for example, endothelial cells can release several other vasodilators and vasoconstrictors such as prostacyclin, endothelin, endothelium-derived hyperpolarizing factor, as well as C-type natriuretic peptides, which may also activate guanylyl cyclase. Therefore, we chose to use the partially isolated guanylyl cyclase preparation to clarify the interaction of inhalational anesthetics and guanylyl cyclase.

Our results, using guanylyl cyclases partially isolated from rat brain, clearly show that inhibition of the NO–guanylyl cyclase pathway by inhalational anesthetics occurs proximal to the activation of both soluble and particulate guanylyl cyclases. In agreement with our study, Eskinder et al. studied the effect of halothane on partially isolated soluble and particulate guanylyl cyclase from canine cerebral arteries and found that 1 mM halothane did not affect the basal soluble guanylyl cyclase activity. In addition, a preliminary study by Van Dyke and colleagues showed that halothane had no effect on basal activity of soluble guanylyl cyclase from rat liver. However, the latter study did show that halothane and isoflurane dose-dependently inhibited the NO-stimulated soluble guanylyl cyclase activity, which disagreed with our results. The reason for this discrepancy is not known, however, they did not include any phosphodiesterase inhibitor in their reaction mixture and they did not add guanosine triphosphate–regenerating system in their reaction mixture, which makes their results difficult to judge.

Although it has been well demonstrated that inhalational anesthetics inhibit the NO–guanylyl cyclase pathway and therefore decrease the cGMP concentrations in tissues, it has also been reported that halothane increases cGMP concentrations in mouse myocardium and cortex, in rat aortas, and in canine cerebral arteries. In support of this, Eskinder et al. demonstrated that a single concentration (3.3%) of halothane stimulated basal particulate guanylyl cyclase activity in their partially isolated enzyme system. However, using a similar system, we could not demonstrate any direct inhibitory or stimulatory effects of inhalational anesthetics on basal or agonist-stimulated particulate guanylyl cyclase activity. The reason for this difference is not apparent, although our work examined a wide concentration range for halothane, enfurane, and isoflurane as well as time dependence of the cyclase assays, and Eskinder et al. studied a single halothane concentration and did not provide any time course data for their enzyme preparations. The disagreement between their findings and ours may also reflect species differences in the action of inhalational anesthetics, although cyclase preparations from a variable tissue beds and species behave quite similarly and the cyclase amino acid sequence is highly homologous across species.

Blaise et al. by using rabbit abdominal aorta and cultured bovine aortic endothelial cells, concluded that halothane may modify either EDRE/NO half-life or its activated oxidation–reduction form, as a means of inhibiting the NO–guanylyl cyclase signaling pathway. However, our data do not agree with Blaise et al.'s conclusion because wide-ranging concentrations of halothane, enfurane, or isoflurane did not inhibit the stimulatory effects of 1 μM of NO on soluble guanylyl cyclase activity and the guanylyl cyclase activity stimulated by different doses of NO was not affected by halothane, enfurane, or isoflurane either. It has been suggested that inhalational anesthetics can affect arterial ring tone by other mechanisms, such as the Ca²⁺-dependent K⁺ channel, apart from the NO–guanylyl cyclase signaling pathway. Therefore it is difficult to isolate the mechanisms that contributed to the effect of halothane on vessel tone in Blaise et al.'s experiments. It is also important to note that the vessel tension in the presence of halothane was always higher than that in the absence of halothane in Blaise et al.'s experiment, no matter whether it was in the presence or absence of NO.

In summary, various doses of halothane, enfurane, and isoflurane did not affect the basal or agonist-stimulated soluble or particulate guanylyl cyclase activity. These results suggest that the activation of guanylyl cyclase by agonists and guanylyl cyclase itself are not the sites of the inhibition of the NO–guanylyl cyclase signaling pathway by inhalational anesthetics. In agreement with the previous studies from our laboratory, inhalational anesthetics appear to inhibit the NO–guanylyl cyclase signaling pathway proximal to activation of guanylyl cyclase.

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