Volatile Anesthetics Inhibit Calcitonin Gene-Related Peptide Receptor-Mediated Responses in Pithed Rats and Human Neuroblastoma Cells

Masataka Kuroda, Daisuke Yoshikawa, Koichi Nishikawa, Shigeru Saito, and Fumio Goto
Department of Anesthesiology, Gunma University Graduate School of Medicine, Maebashi, Japan

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ABSTRACT
Calcitonin gene-related peptide (CGRP) has a potent vasodilatory effect that is mediated by specific receptors predominantly coupled to the activation of adenylate cyclase. The effects of volatile anesthetics on CGPR-induced vasodilation are unclear. We studied the effects of sevoflurane and isoflurane on CGRP-induced vasodilation in pithed rats and CGRP receptor-mediated responses in SK-N-MC cells, which are used as a model system to study the CGRP receptor and its downstream pathways. Male Wistar rats were pithed by inserting a stainless steel rod into the spinal cord. Mean arterial pressure (MAP) and cardiac output were maintained at approximately 100 mm Hg and 50 ml · min⁻¹, respectively, with continuous infusion of noradrenaline. After 30 min of inhalation of anesthetics, CGRP (0.1, 0.3, 1.0, and 3.0 μg/kg) was administered intravenously. In SK-N-MC cells, CGRP-, forskolin-, or cholera toxin-induced cAMP production was measured with or without anesthetics using radioimmunoassays. CGRP receptor binding density and affinity for the agonist were determined with (2-[¹²⁵]Iodohystidyl)CGRP with or without the anesthetics. Sevoflurane (4%) and isoflurane (2%) significantly inhibited the decrease in MAP and systemic vascular resistance. Furthermore, both anesthetics significantly inhibited CGRP- but not forskolin-induced cAMP production. Sevoflurane (4%) and isoflurane (4%) significantly inhibited cholera toxin-induced cAMP production. Both anesthetics did not affect ligand binding. These data suggest that sevoflurane and isoflurane inhibit CGRP-induced vasodilation at the site between the CGRP receptor and adenylate cyclase activation. The inhibitory site of volatile anesthetics on the CGRP receptor-mediated response involves Gₛ protein.

Peripheral vascular tone is maintained primarily by noradrenaline released from sympathetic adrenergic nerve terminals. Nonadrenergic nerves also directly innervate regional vascular beds, and nonadrenergic vasodilation occurs in many species (Bevan and Brayden, 1987). Perivascular nerve stimulation in mesenteric vascular beds induces neurogenic vasodilation; this effect is mediated by nonadrenergic, noncholinergic (NANC) nerves (Kawasaki et al., 1988). Primary afferent neurons, originating from the dorsal root ganglia, provide a perivascular network of fibers around the arterial system throughout the body. Stimulation of these fibers causes NANC vasodilation via the release of calcitonin gene-related peptide (CGRP) (Bell and McDermott, 1996).

CGRP is a 37-amino acid peptide that is generated by alternative RNA splicing processes during calcitonin gene expression in rat and human tissues (Bell and McDermott, 1996). CGRP binds to a specific cell surface receptor, a seven-transmembrane domain receptor protein that belongs to a subgroup of the G protein-coupled receptor family (McLatchie et al., 1998). The receptor is primarily coupled to the activation of adenylyl cyclase, which produces cAMP, leading to smooth muscle relaxation (Bell and McDermott, 1996). CGRP is widely distributed in perivascular nerves throughout the cardiovascular system. It has a potent vasodilatory effect and positive inotropic and chronotropic effects in rat and human (Bell and McDermott, 1996). Intravenous administration of CGRP causes a significant decrease in the mean arterial blood pressure (MAP), total peripheral resistance, and sustained tachycardia in rats and humans (Bell and McDermott, 1996). CGRP is implicated in the regulation of circulatory homeostasis and pathophysiology of various diseases. For example, CGRP is known as a potent vasodilator in brain vessels and has been implicated in the pathogenesis of migraines (Moreno et al., 2002). Increased plasma

ABBREVIATIONS: NANC, nonadrenergic, noncholinergic; CGRP, calcitonin gene-related peptide; CO, cardiac output; GTPyS, guanosine 5’-O-(3-thio)triphosphate; GPCR, G protein-coupled receptor; IBMX, 3-isobutyl-1-methylxanthine; MAP, mean arterial pressure; MEM, minimal essential medium; SVR, systemic vascular resistance.
levels of CGRP have been demonstrated in endotoxia, congestive heart failure (Bell and McDermott, 1996), hepatic cirrhosis (Henriksen et al., 2000), and during cardio-pulmonary bypass (Terazawa et al., 2003). The development of autonomic dysfunction in a mouse model of spinal cord injury is associated with sprouting of CGRP fibers (Jacob et al., 2001). These data suggest that CGRP is responsible for the hemodynamic alterations in these disorders. Because general anesthetics are often used for patients with such disorders, it is important to elucidate the effects of general anesthetics on the CGRP-induced hemodynamic response for better hemodynamic management of complicated patients.

The pithed rat model is used to investigate cardiovascular responses mediated by autonomic outflow from the spinal cord in vivo (Gillespie and Muir, 1967). In pithed animals, there is no intrinsic sympathetic nerve activity or centrally mediated compensatory reflex (Gray et al., 1990). The depressor response during spinal cord stimulation in the pithed rat is attributed to endogenous CGRP released from CGRP-containing nerves (Tuguchi et al., 1992). Volatile anesthetics inhibit NANC depressor responses through inhibition of the CGRP depressor effect, not through inhibition of CGRP release after NANC nerve stimulation in the pithed rat model (Yoshikawa et al., 2003), suggesting that volatile anesthetics inhibit vascular responses to CGRP. Anesthetic actions on cardiac output (CO), systemic vascular resistance (SVR), and CGRP receptor-mediated cellular responses, however, have not yet been studied.

The purpose of the present study was to investigate the effects of volatile anesthetics on 1) CGRP-induced vasodilation by evaluating the changes in hemodynamic parameters, including MAP, CO, and SVR in vivo, and 2) the CGRP receptor-mediated signal transduction pathway in vitro. In the in vivo study, we used a pithed rat model to evaluate the direct vascular effect of drugs without interference of centrally mediated circulatory reflexes. In the in vitro study, we used SK-N-MC human neuroblastoma cells as a model system to study the CGRP receptor and its downstream pathways (Van Valen et al., 1990; Muff et al., 1992; Poyner et al., 1998; Choksi et al., 2002).

Materials and Methods

Animal Preparation

All surgical procedures and experimental protocols were approved by the Gunma University Institutional Animal Care and Use Committee. Surgical procedures were performed as described previously (Shiga and Yoshikawa, 1995; Yoshikawa et al., 1998; 2003). Male Wistar rats weighing 300 to 360 g were anesthetized with isoflurane (Shiga and Yoshikawa, 1995; Yoshikawa et al., 1998; 2003). Male by the Gunma University Institutional Animal Care and Use Com-

Experimental Measurements

MAP was recorded with a Gould (Cleveland, OH) pressure transducer connected to the left carotid artery via a PE-50 catheter. Aortic blood flow was measured using a volume flowmeter (Transonic Systems Inc.). CO and SVR were normalized by the body weight using the following formula: CO = ml · min⁻¹ · kg b.wt.⁻¹ and SVR (mm Hg · ml⁻¹ · min⁻¹ · kg b.wt.⁻¹) = MAP/CO. SVR was determined when MAP and CO reached their minimal values.

Cell Culture

The SK-N-MC cell line was obtained from the American Type Culture Collection (Manassas, VA). The cells were grown in minimal essential medium (MEM) supplemented with 10% fetal bovine serum, 2 mM l-glutamine, 0.1 mM nonessential amino acids, 1 mM sodium pyruvate, 100 U/ml penicillin, and 100 μg/ml streptomycin at 37°C, 95% humidity, and 5% CO₂. For cAMP assays, the cells were seeded on 100-mm culture dishes and grown to confluence. For binding studies, the cells were seeded on 24-well plates at a density of approximately 5 × 10⁴ cells/well and grown to confluence.

Assay of cAMP Production

Equilibration with Volatile Anesthetics. Preincubation with volatile anesthetics was performed as described by Sill et al. (1993) with minor modifications. Serum-free MEM without cells at 37°C (4 ml) was aerated in semiclosed glass vials (5 ml) for 20 min with 95% O₂ and 5% CO₂ gas mixture at 50 ml/min to which volatile anesthetic was added using a calibrated anesthetic vaporizer. After a 20-min equilibration with anesthetics, the gas mixture containing an appropriate concentration of anesthetic was passed continuously over the medium to minimize the loss of anesthetic. The cells (5 × 10⁴ cells/ml) were gently added to the medium at 37°C and preincubated with anesthetic for 20 min before the addition of CGRP or forskolin, a direct adenylate cyclase activator, or cholera toxin, a G₁ protein activator. Gas chromatographic analysis (GC-7A; Shimadzu, Kyoto, Japan) of the media at the end of the protocol indicated that exposure to 1% (v/v) sevoflurane, 2% sevoflurane, 4% sevoflurane, 0.5% isoflu- rane, 1% isoflurane, and 2% isoflurane corresponded to actual concentra- tions of 0.969 ± 0.116, 2.181 ± 0.211, 3.991 ± 0.119, 0.482 ± 0.015, 1.086 ± 0.154, and 1.978 ± 0.155% (v/v), respectively. Cell suspension for control experiments was prepared in the same manner but without anesthetics.

Measurement of cAMP. Suspensions of SK-N-MC cells were used for determining cAMP production. Incubation was terminated by adding 400 μl of 1 N HCl to a 4-ml cell suspension and strong vortexing at the end of each exposure protocol. The mixture was frozen quickly in liquid nitrogen and stored at −70°C until cAMP determination. After thawing, the cell debris in the mixture was pelleted by centrifugation (13,000g for 10 min at 4°C), and the supernatant was transferred to a test tube for the cAMP assay. A cAMP 125I-radioimmunoassay kit (YAMASA Corporation, Choshi, Japan) was used to determine the cAMP levels. All assay procedures were performed according to the manufacturer’s instructions. Data were normalized for protein content using Bradford’s method (Bradford, 1976).

Binding Studies

Equilibration with Volatile Anesthetics. Binding studies were performed at 37°C in an air-tight glass chamber (50 liters) under a continuous flow of a 95% O₂ and 5% CO₂ gas mixture at 3 liters/min, supplemented with 4% sevoflurane or 2% isoflurane using a cali-
brated anesthetic vaporizer. The anesthetic concentrations in the chamber were monitored continuously with a calibrated gas analyzer (Capnomac Ultima; Datex-Ohmeda, Helsinki, Finland). Eagle’s MEM was equilibrated by continuous bubbling with the corresponding concentration of anesthetic for 20 min at 37°C in semiclosed glass vials. Following the preparation, a gas mixture containing the anesthetic was passed continuously over the medium to minimize the loss of anesthetic. Then 1% bovine serum albumin was added to the medium and incubated with anesthetic for 30 min at 37°C. The solution equilibrated with anesthetic was used as the binding buffer. The washing of non-specific binding in the buffer were measured by gas chromatography (GC-7A). Control experiments were performed in the same manner without anesthetic.

**Analysis of Binding Data.** Saturation binding studies were performed using (2-125I)iodohydroxystilbene10) CGRP (2000 Ci/mmol; Amer- sham Biosciences, Ltd., Little Chalfont, Buckinghamshire, UK) at concentrations ranging from 5 to 200 pM per well in the absence (total binding) or presence (non-specific binding) of excessive unlabeled human αCGRP (1 μM) (Peptide Institute, Inc., Osaka, Japan). Specific binding was determined as the difference of total binding and nonspecific binding. Scatchard analysis was used to determine receptor density (Bmax) and the ligand dissociation constant (Kd) (Scatchard, 1949).

**Experimental Protocols**

**Protocol 1: The Effects of Volatile Anesthetics on Hemodynamic Changes Induced by CGRP in Pithed Rat.** Pithed rats were allowed to stabilize for 30 min before any experimental intervention. MAP and CO were maintained at approximately 100 mm Hg and 50 ml • min−1 by continuous infusion of norepinephrine (2 to 3 μg • kg−1 • min−1) throughout the protocol. Rats were randomly assigned to anesthetic groups (n = 7, each) and no anesthetic group (n = 7), and there was a 1-h waiting period after the termination of isoflurane administration to avoid the effects of isoflurane. In the anesthetic groups, a volatile anesthetic (2% sevoflurane, 4% sevoflu- rane, 1% isoflurane, or 2% isoflurane) was administered for 30 min 1 h after pithing. Concentrations of inspired anesthetics were monitored continuously with a calibrated gas monitor (Capnomac Ultima). In the no-anesthetic group, no volatile anesthetic was adminis- tered. Rat αCGRP (0.1, 0.3, 1.0, and 3.0 μg • kg−1; Peptide Institute, Inc.) was administered intravenously for 30 s in 0.1 ml of saline.

**Protocol 2: The Effects of Volatile Anesthetics on cAMP Production in SK-N-MC Cells.** SK-N-MC cells were preincubated for 20 min with or without anesthetics in media containing 0.5 mM 3-isobutyl-1-methylxanthine (IBMX; Sigma-Aldrich, St. Louis, MO) for 20 min with or without anesthetics in media containing 0.5 mM 3-isobutyl-1-methylxanthine (IBMX; Sigma-Aldrich, St. Louis, MO) was administered intravenously for 30 s in 0.1 ml of saline.

**Results**

The Effects of Volatile Anesthetics on CGRP-Induced Hemodynamic Changes in Pithed Rats. Baseline values of hemodynamic parameters and the infusion rates of norepinephrine before the administration of CGRP at 0.1 μg/kg in control group were as follows: MAP = 109.0 ± 4.6 mm Hg, CO = 154.1 ± 6.3 ml • min−1 • kg−1, SVR = 0.709 ± 0.05 mm Hg • ml−1 • min−1 • kg−1, and norepinephrine = 2.2 ± 0.9 μg • kg−1 • min−1, respectively. There was no significant difference in these data among groups (data not shown). Consistent with our previous reports, Intravenously administered CGRP induced a transient increase in MAP followed by a persistent decrease. MAP and CO changed similarly. MAP and CO maximally increased immediately after injection of CGRP and reached the minimal value ap- proximately 1 min after injection of CGRP. SVR also decreased approximately 1 min after administration of CGRP. Injection of saline had no effect.

The effects of sevoflurane on CGRP-induced changes of the hemodynamic parameters are shown in Fig. 1. Sevoflurane significantly inhibited CGRP-induced increases in MAP (p < 0.01, n = 7). On the other hand, CGRP induced a dose-dependent decrease in MAP, CO, and SVR. Sevoflurane concentration dependently inhibited the CGRP-induced decrease in MAP and SVR (p < 0.05, n = 7). The decrease in CO did not differ significantly among groups. Heart rate did not change significantly after administration of CGRP in either group. Isoflurane also inhibited CGRP-induced increases in MAP (p < 0.05, n = 7) and dose dependently inhibited CGRP-induced decreases in MAP and SVR (p < 0.05, n = 7) without effects on CO reduction and HR (data not shown).

The Effects of Volatile Anesthetics on CGRP-, Forskolin-, or Cholera Toxin-Induced cAMP Production in SK-N-MC Cells. Sevoflurane did not alter basal cAMP accumulation (Fig. 2A). The effect of sevoflurane on CGRP-induced cAMP production is shown in Fig. 2B. CGRP (10−7 M) increased cAMP production in SK-N-MC cells (20-fold increase over basal). Preincubation of cells with sevoflurane concentration dependently inhibited CGRP-induced cAMP production. Sevoflurane (4%) significantly inhibited CGRP-induced cAMP production to 35% of no anesthetic (p < 0.01, n = 6). Forskolin (10−6 M) increased cAMP production in SK-N-MC cells (25-fold increase over basal), whereas preincubation with sevoflurane did not influence the forskolin-induced increase in cAMP (Fig. 2C). Preincubation of cells with isoflurane also caused a concentration-dependent reduction in CGRP-induced cAMP production. Isoflurane (2% or 4%) significantly inhibited CGRP-induced cAMP production to 46% of no anesthetic (p < 0.05, n = 6) or to 27% (p < 0.01,
respectively, whereas preincubation with isoflurane did not alter forskolin-induced cAMP production (data not shown).

The effects of sevoflurane on time-dependent cholera toxin-induced cAMP production in SK-N-MC cells were shown in Fig. 3 (inset). After a lag of 15 min, cholera toxin (10^{-9} M) exhibited time-dependent increases in cAMP production in each group. Sevoflurane (4%) significantly inhibited cholera toxin-induced cAMP production at 90 and 120 min (Fig. 3 (inset); \( p < 0.05, n = 6 \)). Dose dependence of sevoflurane on cholera toxin-induced cAMP production was shown in Fig. 3. Sevoflurane did not affect basal cAMP production (data not shown). Cholera toxin (10^{-9} M) increased cAMP production in SK-N-MC cells (30-fold increase over basal). Sevoflurane dose dependently inhibited cholera toxin-induced cAMP production. Sevoflurane (4%) significantly inhibited cholera toxin-induced cAMP production to 70% of no anesthetic (\( p < 0.05, n = 6 \)). Isoflurane (2%) had no effect on \( B_{\text{max}} \) and \( K_d \) when compared with no anesthetic and sevoflurane.

Radioligand Binding Studies. Specific binding of \(^{125}\text{I}-\text{CGRP}\) to SK-N-MC cells was saturable with increasing concentration of \(^{125}\text{I}-\text{CGRP}\) (5–200 pM). The receptor density (\( B_{\text{max}} \)) and the ligand dissociation constant (\( K_d \)) calculated from plots according to the method of Scatchard are shown in Table 1. There was no significant difference in \( B_{\text{max}} \) and \( K_d \) among groups. Preincubation with 4% sevoflurane did not affect CGRP receptor density and affinity. Isoflurane (2%) had no effect on \( B_{\text{max}} \) and \( K_d \) when compared with no anesthetic and sevoflurane.

Discussion

The major findings of the present study are summarized below. Sevoflurane and isoflurane, at clinically relevant concentrations, dose dependently inhibited the CGRP-induced increase in MAP and the decrease in MAP and SVR in pithed rats. Sevoflurane and isoflurane inhibited CGRP-induced cAMP production in a dose-related manner in SK-N-MC cells. Neither anesthetic had an effect on forskolin-induced cAMP production in the cells nor inhibited ligand binding to the CGRP receptor. Furthermore, both anesthetics dose dependently inhibited cholera toxin-induced cAMP production in the cells. These data suggest that both anesthetics inhibit CGRP-induced vasodilation by interfering with the signal transduction pathway between CGRP receptors and adenylate cyclase. The inhibitory site of volatile anesthetics on CGRP receptor-mediated response involves \( G_{\alpha} \) protein.

The Effects of Volatile Anesthetics on CGRP-Induced Hemodynamic Changes in Pithed Rats. Yoshikawa et al. (2003) reported that isoflurane and halothane inhibited the NANC depressor response in pithed rats. Although isoflurane, halothane, and sevoflurane did not affect CGRP release after spinal cord stimulation, isoflurane and halothane inhibited the depressor response to exogenously administered CGRP. These results suggest that volatile anesthetics inhibit the NANC depressor response by inhibiting the CGRP depressor effect but not by inhibiting CGRP release.

In a pithed rat model, we investigated not only the effect of volatile anesthetics on CGRP-induced changes in blood pressure but also the CGRP-induced vasodilation by measuring SVR, which reflects the systemic vascular tone. Sevoflurane (4%) and isoflurane (2%) significantly inhibited the CGRP-induced decrease in SVR. Lower concentrations of volatile anesthetics (2% sevoflurane and 1% isoflurane) did not affect the decrease in SVR.

In general, there are four main mechanisms of the vasodepressor response elicited by intravenous drug administration: 1) central nervous system actions, 2) inhibition of vascular sympathetic transmission, 3) release of endothelium-derived relaxing factors, and 4) direct vasorelaxing effects (Saxena and Villalon, 1990). Both central and autonomic nervous system activity were excluded by using pithed va-
gotomized rats. Therefore, CGRP-induced vasodilatory effects in the present study were mediated by actions on the vascular endothelium (releasing relaxing factors) and/or the vascular smooth muscle cells (producing direct relaxation). CGRP, among the most potent vasodilating substances known, also exerts positive inotropic effects (van Rossum et al., 1997). These biologic responses are mediated by specific cell surface receptors predominantly coupled to the activation of adenylate cyclase (van Rossum et al., 1997). In the current study, 4% sevoflurane and 2% isoflurane inhibited the CGRP-induced vasodilatory effects. In addition, 4% sevoflurane and 2% isoflurane inhibited the increase in MAP after CGRP administration, suggesting that high concentrations of volatile anesthetics inhibit both vasodilatory and positive inotropic effects induced by CGRP. These data strongly suggest that volatile anesthetics inhibit the CGRP-induced response through an effect on CGRP receptor-mediated responses.

**The Effects of Volatile Anesthetics on CGRP Receptor-Mediated Signal Transduction in SK-N-MC Cells.**

CGRP relaxes vascular smooth muscle cells via both endothelium-dependent and endothelium-independent signal transduction pathways (Bell and McDermott, 1996). These responses are mediated by the specific cell surface family B G protein-coupled receptor (GPCR) and the calcitonin receptor-like receptor (McLatchie et al., 1998). The receptor is predominantly coupled to the activation of adenylate cyclase, which produces cAMP, leading to vascular relaxation in both pathways. In addition, there are other mechanisms by which CGRP elevates nitric oxide directly without the involvement of adenylate cyclase or activates ATP-sensitive potassium channels (K$_{ATP}$) (Bell and McDermott, 1996). On the other hand, CGRP-mediated inotropic action in the myocardium is mediated through CGR receptors (van Rossum et al., 1997). In the present study, sevoflurane and isoflurane significantly inhibited CGRP-induced cAMP production but had no effect on for-
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skolin-induced cAMP production. Neither anesthetic had an effect on CGRP receptor binding. Furthermore, sevoflurane and isoflurane significantly inhibited cholina toxin-induced cAMP production. Therefore, sevoflurane and isoflurane inhibited CGRP receptor-mediated signal transduction at the step between the CGRP receptor and adenylate cyclase activation by interfering with the activation of G protein.

Volatile anesthetics are likely to affect several hydrophobic sites within the cell membrane, particularly membrane-binding proteins (Franks and Lieb, 1994). Possible sites of the action of anesthetics in the GPCR-mediated signal transduction pathway are divided into four target groups: 1) agonist-receptor binding, 2) G protein function, 3) effector activity (adenylate cyclase), and 4) other intracellular sites (e.g., Ca\(^{2+}\) stores and cellular kinases) (Lambert, 1993).

There are no previous reports demonstrating an effect of volatile anesthetics on CGRP receptor-mediated signal transduction, although several studies reported that volatile anesthetics affect the signal transduction pathway mediated by other GPCRs. For example, halothane and isoflurane attenuate isoproterenol-induced vasodilation and interfere with β-adrenoceptor-mediated responses in the rat aorta at a point between agonist-receptor binding and adenylyl cyclase activation (Tanaka and Tsuchida, 1998). Pentyala et al. (1999) reported that volatile anesthetics, including sevoflurane and isoflurane at clinically relevant doses, modulate the binding of guanine nucleotides to purified Gs subunits in aqueous solution, inhibiting the exchange of a nonhydrolyzable analog of guanosine 5′-triphosphate (GTP\(^{\gamma}\)S) for bound guanosine 5′-diphosphate (GDP). This finding suggested that volatile anesthetics directly affect the guanine nucleotide binding site, including the Gs subunit. These studies are consistent with our current study and support the notion that sevoflurane inhibits the GPCR-mediated signal transduction pathway at the G protein level. Furthermore, cholina toxin affects G protein by ADP ribosylating the α-subunit of Gs. ADP ribosylation of the Gs by cholera toxin stabilizes the GTP-bound conformation of Gs and decreases its intrinsic GTPase activity, resulting in the persistent activation of adenylyl cyclase (Neer and Clapham, 1988). In the current study, sevoflurane and isoflurane dose-dependently inhibited cholina toxin-induced cAMP production, suggesting that both anesthetics might affect the conformation and stability of the GTP-bound state of Gs and/or GTPase activity.

On the other hand, volatile anesthetics interfere with muscarinic receptor-G protein interactions in rat brainstem (Anthony et al., 1989). Sevoflurane depresses the β-adrenoceptor-mediated signal transduction in rat myocardium by reducing ligand-receptor binding and disrupting the relation between the receptor and G protein (Sanuk et al., 1994). Halothane, which inhibits receptor-activated Gprotein-coupled pathways in airway smooth muscle cells, must functionally target a component of the G protein-coupled receptor complex other than Gs (Streff et al., 2003). These studies suggest that volatile anesthetics might inhibit the GPCR-mediated signal transduction pathway at the receptor itself or the interaction between the receptor and G protein. In the current study, isoflurane significantly inhibited CGRP-induced cAMP production at 2%, whereas isoflurane significantly inhibited cholina toxin-induced cAMP production at 4%. Therefore, in addition to G protein, isoflurane might inhibit GPCR receptor-mediated signal transduction between the receptor and the G protein.

In the present study, we focused on CGRP actions in rat hemodynamic system. CGRP is widely distributed in the body, including the nervous and gastrointestinal systems. Further studies elucidating CGRP actions in multiple organs may be indispensable to fully understand the roles of CGRP in the body and the importance of circulating cAMP levels in the plasma.

In conclusion, sevoflurane and isoflurane inhibit CGRP-induced positive inotropic and vasodilatory effects in pithed rats. Both anesthetics inhibited CGRP- and cholera toxin-induced cAMP production. Both anesthetics did not affect forskolin-induced cAMP production and 125\(^{I}\)-GTP ligand-receptor binding in SK-N-MC cells. These results suggest that the inhibitory site of volatile anesthetics on the GPCR receptor-mediated signal transduction involves G protein.

References


Address correspondence to: Masataka Kuroda, Department of Anesthesiology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi City 371-8511, Japan. E-mail: mkuroda@med.gunma-u.ac.jp