

The Diverse Actions of Volatile and Gaseous Anesthetics on Human-cloned 5-Hydroxytryptamine₃ Receptors Expressed in *Xenopus* Oocytes

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Background: General anesthetics can modulate the 5-hydroxytryptamine type 3 (5-HT₃) receptor, which may be involved in processes mediating nausea and vomiting, and peripheral nociception. The effects of the new volatile anesthetic sevoflurane and the gaseous anesthetics nitrous oxide (N₂O) and xenon (Xe) on the 5-HT₃ receptor have not been well-characterized.

Methods: Homomeric human-cloned 5-HT_{3A} receptors were expressed in *Xenopus* oocytes. The effects of halothane, isoflurane, sevoflurane, N₂O, and Xe on 5-HT-induced currents were studied using a two-electrode, voltage clamping technique.

Results: Halothane (1%) and isoflurane (1%) potentiated 1 μM 5-HT-induced currents to 182 ± 12 and 117 ± 2%, respectively. In contrast, sevoflurane (1%), N₂O (70%), and Xe (70%) inhibited 5-HT-induced currents to 76 ± 1, 77 ± 4, and 34 ± 4%, respectively. The inhibitory effects were noncompetitive for sevoflurane and competitive for N₂O and Xe. None of these inhibitory effects showed voltage dependency.

Conclusion: Inhalational general anesthetics produce diverse effects on the 5-HT₃ receptor. Both halothane and isoflurane enhanced 5-HT₃ receptor function in a concentration-dependent manner, which is consistent with previous studies. Sevoflurane inhibited the 5-HT₃ receptor noncompetitively, whereas N₂O and Xe inhibited the 5-HT₃ receptor competitively, suggesting the inhibitory mechanism of sevoflurane might be different from those of N₂O and Xe.

THE 5-hydroxytryptamine type 3 (5-HT₃) receptor is a member of the superfamily of ligand-gated ion channel receptors sharing structural similarities with the nicotinic acetylcholine, glycine, and γ-aminobutyric acid type A (GABA_A) receptors.¹ Most receptors of this superfamily are modulated by general anesthetics.² The 5-HT₃ receptors are diffusely distributed in both the central and peripheral nervous system and are involved in physiologic and pathologic processes mediating nausea and vomiting, peripheral nociception, and central antinociception.³ Volatile and intravenous anesthetics and alcohol can variously modulate 5-HT₃ receptor function.⁴⁻⁷ Volatile anesthetics and alcohol potentiate 5-HT₃ receptor function,^{4,5} whereas intravenous anesthetics, such as

pentobarbital⁶ and propofol,⁷ inhibit 5-HT₃ receptor function. Because one of the physiologic effects of anesthetics is modulation of the 5-HT₃ receptor, the enhancement of 5-HT₃ receptor responses by volatile anesthetics has been suggested as the underlying mechanism of postoperative nausea and vomiting (PONV).⁸ Taken together with the fact that specific 5-HT₃ receptor antagonists, such as ondansetron, may alleviate PONV,⁹⁻¹¹ the potentiation of the 5-HT₃ receptor by volatile anesthetics might be associated with the mechanism of PONV. However, the effects on the 5-HT₃ receptor of gaseous anesthetics, such as nitrous oxide (N₂O), which is widely used in clinical practice, and xenon (Xe), which has recently been focused on for clinical use, have not been well-characterized.¹² In this study, we used electrophysiologic techniques to examine and compare the effects of three volatile anesthetics (halothane, isoflurane, and sevoflurane) and two gaseous anesthetics (N₂O and Xe) on cloned human 5-HT_{3A} receptors expressed in *Xenopus* oocytes.

Materials and Methods

Expression of Human 5-HT_{3A} Receptor in *Xenopus* Oocytes

Human-cloned 5-HT_{3A} complementary DNA (cDNA) was kindly provided by Akira Miyake, Ph.D. (Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Ibaragi, Japan).¹³ The cDNA encoding the human 5-HT_{3A} receptor was subcloned into pBluescriptII (Stratagene, La Jolla, CA) and was linearized by EcoRI (Wako Pure Chemical Industries, Ltd., Osaka, Japan) to create the template cDNA. Capped complementary RNA (cRNA) was synthesized *in vitro* from cDNA using T₃ RNA polymerase (T3 mMESSAGE mMACHINE KIT; Ambion, Austin, TX) according to the manufacturer's instructions. In accordance with the study protocol approved by the Animal Research Committee of Osaka University Medical School (Osaka, Japan), female *Xenopus laevis* were anesthetized on ice with 1% 3-aminobenzoic ethyl ester (Tricaine; Sigma, St. Louis, MO). Oocytes were harvested through a laparotomy incision, manually defolliculated with forceps, and treated with 1.5 mg/ml collagenase type 1A (Sigma) for 30 min at room temperature in modified Barth saline (MBS: 88 mM NaCl, 1 mM KCl, 10 mM HEPES, 1 mM MgCl₂, 2.4 mM NaHCO₃; pH 7.4). Between 10 and 50 ng cRNA was injected into an oocyte with a glass capillary, using a

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Nanoject injector (Drummond Scientific, Broomall, PA). Oocytes were incubated at 20°C in MBS containing 1.8 mM Ca^{2+} until the start of the electrophysiologic experiment.

Electrophysiology

Between 24 and 48 h after cRNA injection, the oocytes were placed in a 0.2-ml chamber and were continuously superfused with MBS containing 1.8 mM CaCl_2 at 5–10 ml/min. The electrophysiologic recordings were made using a two-electrode, voltage clamp technique. The oocytes were impaled with 1- to 5-M Ω electrodes filled with 3 M KCl solution and were voltage clamped at –70 mV (CEZ-1250; Nihon Kohden, Tokyo, Japan). Drugs were dissolved in MBS and applied to the perfusate. Volatile and gaseous anesthetics were added to the perfusate by bubbling anesthetic-containing gases with or without 5-hydroxytryptamine (5-HT). A 50-ml conical tube (Corning 430291; Corning, NY) was filled with solution, and anesthetic gases were continuously bubbled into the tube at a rate of 100 ml/min. For volatile anesthetics (halothane, isoflurane, and sevoflurane), the air was passed through the following calibrated vaporizers: Fluotec3 for halothane (Ohmeda, Steeton, West Yorkshire, United Kingdom), Forawick for isoflurane (Murako Medical, Tokyo, Japan) and Sevotec3 for sevoflurane (Ohmeda). For gaseous anesthetics (N_2O and Xe), gas mixtures at different concentrations of each gas were prepared using precise flowmeters (PMG-1; KOFLOC Co., Ltd., Kyoto, Japan). The concentrations of N_2O and Xe in the gas mixtures were measured using a Datex Capnomac Ultima (Datex Instrumentarium Corp., Helsinki, Finland) and a Xe meter (Riken, Tokyo, Japan), respectively. The concentration of oxygen or nitrogen in the control solution was adjusted to the same level as the oxygen concentration in the anesthetic solution. Anesthetic solutions were bubbled with the anesthetic-containing gas mixture for 30 min. Anesthetic solutions were preapplied to oocytes before exposure to 5-HT to allow time for equilibrium. Each drug application was separated by intervals of a few minutes and by longer intervals after application of high drug concentrations to eliminate receptor desensitization. Cumulative desensitization was excluded by confirming that the same response was induced by a low concentration of 5-HT during an experiment with one oocyte. The current was digitally recorded using AxoScope software (Axon Instruments, Burlingame, CA), running on an IBM personal computer (IBM Aptiva, Armonk, NY). All electrophysiologic experiments were performed at room temperature.

Determination of Anesthetic Concentration in Solutions

The different concentrations of volatile and gaseous anesthetics in solution were determined by gas chromatography-mass spectrometry-selected ion monitoring

(GC-MS-SIM).^{14,15} A gas chromatograph (Trace GC2000, ThermoQuest; CE Instruments, Austin, TX) and mass spectrometer (GCQ plus, ThermoQuest; CE Instruments) equipped with a data processing system (Xcaliber, ThermoQuest; CE Instruments) were used. The capillary column used was DB-5MS (0.25 mm ID \times 30 m; J&W Scientific, Folsom, CA). Using the head space sampling technique,¹⁴ the concentrations of anesthetic in the solution and gas phase were measured using an automatic gas sampler (COMBI PAL; CTC Analytics AG, Zwingen, Switzerland). The ion intensities of isoflurane, sevoflurane, N_2O , and Xe were monitored using mass/charge values (m/z) of 51, 51, 30, and 129, respectively. The anesthetic peak spectra areas were measured and compared to determine the gas/MBS partition. The gas/solution partition coefficient (P) of each anesthetic at 25°C was calculated using the following equation: $P = C_{\text{Ring}}/C_{\text{gas}}$, where C_{gas} and C_{Ring} are the equilibrated concentrations of anesthetic in the gas phase and MBS. Then the actual concentration of each anesthetic in the experimental solution was determined by using the absolute calibration curve established for each anesthetic in solution.

Data Analysis

Peak amplitudes of the current elicited by the drugs were measured directly from digital recordings stored in AxoScope. To obtain the concentration–response curve for 5-HT-induced currents, observed peak amplitudes were normalized and plotted and then fitted to the Hill equation below using Sigmaplot software (Jandel Scientific, San Rafael, CA):

$$I = I_{\text{max}} / (1 + (EC_{50}^n / [5\text{-HT}]^n))$$

where I is the peak current at a given concentration of 5-HT, I_{max} is the maximum current, EC_{50} is the concentration of 5-HT eliciting a half-maximum response, and n denotes the Hill coefficient.

Statistical analyses were performed using the Student t test, with significance levels set at $P < 0.05$. All data were expressed as mean \pm standard error of the mean.

Chemicals

5-Hydroxytryptamine was purchased from Wako Pure Chemical Industries, Ltd. The selective 5-HT₃ antagonist ramosetron was donated by the Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd. The anesthetics were sourced as follows: halothane (Takeda Chemical Industries, Osaka, Japan), isoflurane (Abbott Laboratories Ltd., Chicago, IL), sevoflurane (Maruichi Pharmaceutical Co., Ltd., Osaka, Japan), N_2O (Teisan Ltd., Tokyo, Japan), and Xe (99.995%; AirWater Co. Ltd., Wakayama, Japan).

Table 1. The Gas/MBS Partition Coefficient at 25°C and the Actual Anesthetic Concentrations of MBS Used

	Partition Coefficient	Actual Anesthetic Concentrations (mM)						
		0.5%	1%	2%	4%	35%	70%	100%
Halothane	1.12 ± 0.02	0.21 ± 0.00	0.41 ± 0.02	0.86 ± 0.01	1.7 ± 0.1			
Isoflurane	1.04 ± 0.01	0.23 ± 0.01	0.48 ± 0.02	0.94 ± 0.03	2.0 ± 0.0			
Sevoflurane	0.63 ± 0.01	0.24 ± 0.00	0.45 ± 0.01	0.89 ± 0.02	1.8 ± 0.1			
N ₂ O	0.94 ± 0.03					13 ± 0	26 ± 0	37 ± 0
Xe	0.12 ± 0.01					1.6 ± 0.1	3.5 ± 0.1	4.7 ± 0.1

Data are expressed as mean ± standard error of the mean (n ≥ 3).

MBS = modified Barth saline.

Results

The gas/MBS partition coefficient of each anesthetic at 25°C was calculated based on measurements made using GC-MS-SIM, and was 1.12 ± 0.02 for halothane, 1.04 ± 0.01 for isoflurane, 0.63 ± 0.01 for sevoflurane, 0.94 ± 0.03 for N₂O, and 0.12 ± 0.01 for Xe. The actual concentrations of the anesthetics in the MBS used in this study are summarized in table 1.

We confirmed that the 5-HT-induced currents in oocytes injected with human 5-HT_{3A} receptor cRNA were reversibly blocked by the selective 5-HT₃ receptor antagonist ramosetron (data not shown). The peaks of the 5-HT-induced currents were concentration dependent, and the 5-HT concentration-response curve fitted well to the Hill equation, with an EC₅₀ of 2.7 ± 0.1 μM and a Hill coefficient of 1.7 ± 0.1.

Applications of all volatile (up to 4%) and gaseous (up to 100%) anesthetics without 5-HT produced no detectable current (data not shown). To exclude the involvement of oxygen and nitrogen concentrations in the 5-HT-induced current, we evaluated the effects of the perfusates, which contain 5-HT under various concentrations of these gases (0-100%). The control currents induced by 5-HT were not affected by the concentration of oxygen or nitrogen in the perfusate (data not shown). Figure 1 shows the traces of 5-HT-induced currents potentiated and inhibited by the anesthetics. The potentiation and inhibition by the anesthetics were fully reversible. The volatile anesthetics halothane and isoflurane potentiated the 5-HT-induced current at clinical concentrations. The currents induced by 1 μM 5-HT, which was equivalent to EC₁₅, were enhanced by 0.5, 1, 2, and 4% halothane to 154 ± 9, 182 ± 12, 196 ± 15, and 263 ± 14%, and by 0.5, 1, 2, and 4% isoflurane to 110 ± 2, 117 ± 2, 132 ± 4, and 151 ± 8%, respectively. Halothane potentiated the 5-HT-induced current to a larger degree than did isoflurane at the same concentration. In contrast, the volatile anesthetic sevoflurane and the gaseous anesthetics N₂O and Xe inhibited 5-HT-induced currents. Sevoflurane reduced 1 μM 5-HT-induced currents to 89 ± 2, 76 ± 1, 56 ± 3, and 33 ± 2% at concentrations of 0.5, 1, 2, and 4%, respectively. N₂O inhibited the current to 88 ± 1, 77 ± 4, and 64 ± 3%,

and Xe inhibited the current to 51 ± 3, 34 ± 4, and 21 ± 4% at concentrations of 35, 70, and 100%, respectively. Xe inhibited the current more potently than did N₂O over the range of concentrations tested. These potentiating and inhibitory effects by anesthetics on 5-HT-induced currents were all concentration dependent (fig. 2).

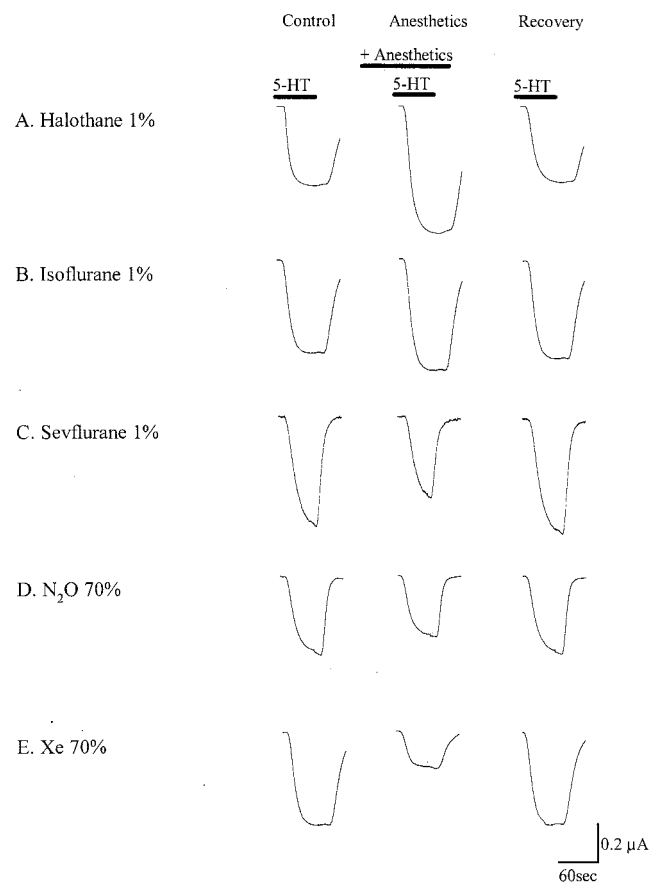


Fig. 1. Effects of anesthetics on 5-hydroxytryptamine (5-HT)-induced currents in the 5-HT₃ receptor. One percent halothane (A) and 1% isoflurane (B) potentiated the 5-HT₃ receptor, but 1% sevoflurane (C), 70% N₂O (D), and 70% Xe (E) reversibly inhibited 1 μM (EC₁₅: agonist concentration giving 15% of maximal response) 5-HT-induced currents. The horizontal bars indicate the duration of application of the drugs. Anesthetic solutions were preperfused for 30 s before application of an anesthetic-containing 5-HT solution.

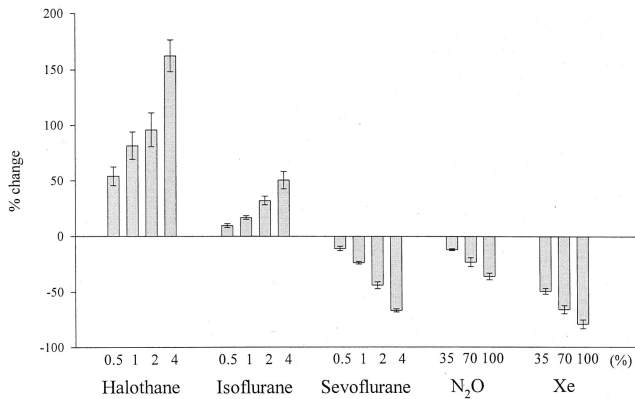


Fig. 2. Concentration-dependent effects of anesthetics on 5-hydroxytryptamine (5-HT)-induced currents in the 5-HT₃ receptor. The study compared the effects on 1 μ M 5-HT (EC₁₅)-induced currents of anesthetics at concentrations of 0.5, 1, 2, and 4% halothane, isoflurane, and sevoflurane and at concentrations of 35, 70, and 100% N₂O and Xe. Values are expressed as percent of the control response without anesthetics. Halothane and isoflurane potentiated the 5-HT₃ receptor, but sevoflurane, N₂O, and Xe inhibited 5-HT-induced currents in a concentration-dependent manner ($P < 0.05$ vs. control). Data from more than five oocytes were expressed as mean \pm standard error of the mean.

The concentration-response curves of 5-HT were obtained in the absence and presence of 1% sevoflurane, 100% N₂O, and 100% Xe, respectively (fig. 3). Sevoflurane reduced the maximal response without changing the EC₅₀ values (2.7 ± 0.1 and 2.8 ± 0.2 μ M, respectively), but N₂O and Xe shifted the concentration-response curves of 5-HT to the right without changing the maximal responses. The EC₅₀ value of 5-HT was shifted to 4.0 ± 0.4 μ M for N₂O and to 4.1 ± 0.2 μ M for Xe. These data indicate that these anesthetics inhibit the 5-HT₃ receptor according to different mechanisms, with sevoflurane acting noncompetitively and N₂O and Xe acting competitively. The inhibitory effects of these three anesthetics were also examined at various membrane potentials. The effects of 2% sevoflurane, 70% N₂O, and 70% Xe were not significantly different for membrane potentials ranging from -90 mV to $+30$ mV (Student *t* test, $P > 0.05$) (fig. 4).

Discussion

The 5-HT₃ receptor belongs to the superfamily of ligand-gated ion channels, which includes the nicotinic acetylcholine (nACh), glycine, and GABA_A receptors.¹ Two 5-HT₃ receptor subunits, 5-HT_{3A}¹⁶ and 5-HT_{3B},¹⁷ have been identified. The 5-HT_{3A} subunit has been cloned from various species (mouse, rat, human) and can exist as a homomeric receptor in some systems (*e.g.*, mouse neuroblastoma N1E-115 and dorsal root ganglion neurons). The heteromeric receptor, comprising 5-HT_{3A} and 5-HT_{3B} subunits, can exist in some regions of the brain and displays distinctive pharmacologic properties,

especially with an antagonist such as tubocurarine.¹⁷ Although there is no information available about the pharmacologic difference between the effect of anesthetics on homomeric and heteromeric 5-HT₃ receptors, research into anesthetic effects in the heteromeric 5-HT₃ receptor may be necessary to provide a better understanding of the clinical significance of the effect of anesthetics on the 5-HT₃ receptor. Miyake *et al.* reported interspecies differences not only in terms of structure but also in terms of tissue distribution and pharmacologic profile.¹³ The affinity of the human 5-HT₃ receptor for the 5-HT₃ receptor agonist *m*-chlorophenylbiguanide was much lower than that seen in the rat 5-HT₃ receptor, and 2-methyl-5-HT, a partial agonist for the mouse 5-HT₃ receptor, was a full agonist for the human 5-HT₃ receptor.¹³ In native neurons, the dissociative anesthetic ketamine potentiated 5-HT₃ receptor function in a rabbit nodose ganglion neuron at clinical concentrations.¹⁸ Ketamine at similar concentrations failed to

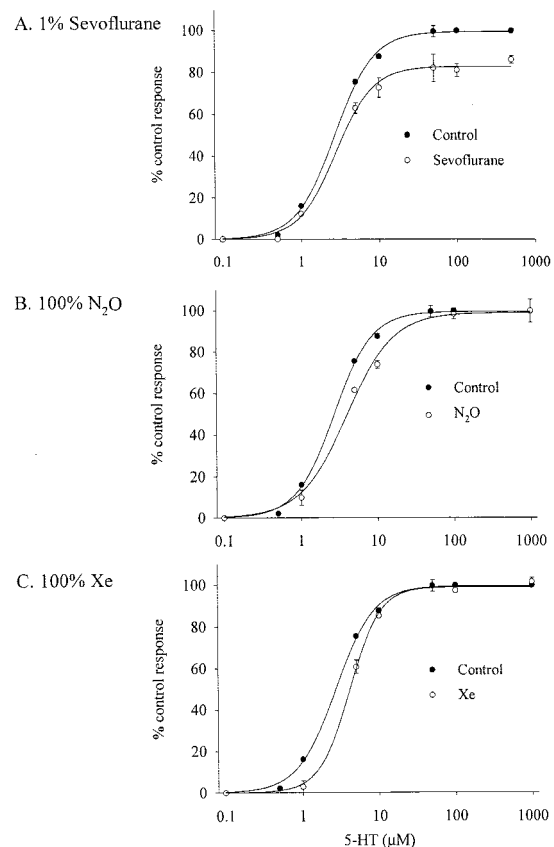


Fig. 3. Normalized 5-hydroxytryptamine (5-HT) concentration-response curves with or without 1% sevoflurane (A), 100% N₂O (B), and 100% Xe (C). Sevoflurane reduced the maximal 5-HT-induced current responses without changing the EC₅₀ values (2.7 ± 0.1 μ M for the control vs. 2.8 ± 0.2 μ M for sevoflurane). N₂O and Xe shifted the 5-HT-induced concentration-response curves to the right without changing the maximal responses. The EC₅₀ value of 5-HT increased to 4.0 ± 0.4 μ M for N₂O and to 4.1 ± 0.2 μ M for Xe. Data from more than five oocytes were expressed as mean \pm standard error of the mean.

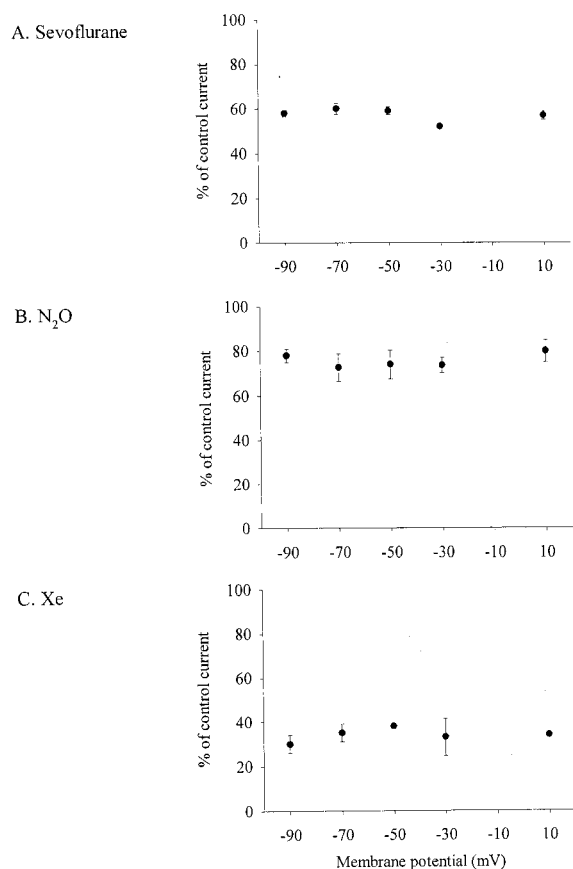


Fig. 4. Effects of anesthetics on 5-hydroxytryptamine (5-HT)-induced currents at different membrane potentials ranging from -90 to $+30$ mV. The percentages of the control currents were plotted. (A) $1 \mu\text{M}$ 5-HT with 2% sevoflurane. (B) $1 \mu\text{M}$ 5-HT with 70% N_2O . (C) $1 \mu\text{M}$ 5-HT with 70% Xe. No significant difference ($P > 0.05$ vs. percent of control current at -70 mV) was found at different membrane potentials, showing no voltage dependency. Data from more than five oocytes were expressed as mean \pm standard error of the mean.

modulate recombinant murine 5-HT₃ receptor expressed in oocytes, whereas high concentrations produced inhibition of function.¹⁹ Therefore, the pharmacologic responses of the 5-HT₃ receptors to anesthetics seem to differ among species. Our data showed 1% (0.41 mM) halothane and 1% (0.48 mM) isoflurane potentiated $1 \mu\text{M}$ (EC_{15}) 5-HT-induced currents of a human recombinant 5-HT₃ receptor to 181.9 and 116.9%, respectively. These results were consistent with those of previous reports. Machu *et al.*⁵ reported $0.75 \mu\text{M}$ 5-HT-induced currents of a NCB-20 recombinant 5-HT₃ receptor were potentiated by 0.15 mM halothane and isoflurane to 133 and 111%, respectively. Jenkins *et al.*⁴ reported that in N1E-115 neuroblastoma cells, 0.21 mM halothane, and 0.31 mM isoflurane potentiated $1 \mu\text{M}$ 5-HT-induced currents to almost 150 and 115%. The larger potentiations with halothane than with isoflurane at clinically relevant concentrations were found in 5-HT₃ receptors from various species. Anesthetic action on the 5-HT_{3A} receptor seems to show no difference between species.

The 5-HT₃ receptor has received considerable attention recently in relation to general anesthetics.²⁰ Most volatile anesthetics, such as halothane, isoflurane, enflurane, and methoxyflurane, at clinical concentrations potentiated 5-HT-induced currents in 5-HT₃ receptors in N1E-115 neuroblastoma cells and recombinant 5-HT₃ receptors expressed in oocytes.^{4,5,13} Intravenous anesthetics, such as thiopental, etomidate, alfaxalone, and propofol, inhibited 5-HT₃ receptor-mediated currents in N1E-115 cells,^{7,21} whereas propofol has been shown to have no significant effect at clinical concentrations in recombinant 5-HT_{3A} receptors.⁵ Jenkins *et al.*⁴ reported diverse effects of n-alcohols on the 5-HT₃ receptor; the lower alcohols, such as butanol and hexanol, potentiated the 5-HT₃ receptor at low concentrations but inhibited it at high concentrations, and the higher alcohols, such as octanol and decanol, inhibited the 5-HT₃ receptor at any concentration. Little is known about the effects of gaseous anesthetics, such as N_2O and Xe, on the 5-HT₃ receptor. Recently, Yamakura *et al.*¹² reported that a recombinant 5-HT₃ receptor was slightly inhibited by N_2O . N_2O and Xe had a similar type of effect on other ligand-gated ion channels, although there are no data available about the interaction between Xe and the 5-HT₃ receptor. According to the results of this study, isoflurane and halothane had a potentiating effect on the 5-HT₃ receptor, whereas sevoflurane, N_2O , and Xe produced inhibitory effects. Like other ligand-gated ion channels, the 5-HT₃ receptor can be directly modulated by general anesthetics, but it produces diverse effects. Interestingly, this is in contrast to the effect on the GABA_A receptor, which is potentiated by most anesthetics.²

It is interesting to note that the inhibitory effects of N_2O and Xe on the 5-HT₃ receptor are competitive with no voltage dependency, whereas that of sevoflurane is noncompetitive. The evidence that both thiopental⁴ and alfaxalone²¹ inhibit the 5-HT₃ receptor in a noncompetitive manner suggests that sevoflurane may share a similar inhibitory mechanism of action with these anesthetics. Yamakura *et al.*¹² investigated the effects of N_2O and Xe on several kinds of ligand-gated ion channels, and the inhibition of NMDA and nACh receptors by N_2O was noncompetitive with the voltage dependencies. It has been reported that the inhibitory mechanism of Xe was also noncompetitive for the NMDA receptor.²² The mechanisms of action of N_2O and Xe at the 5-HT₃ receptor might be different from those at the NMDA and nACh receptors. The molecular determinant of the sensitivities to N_2O and Xe has been identified in the nACh receptor²³ as a single amino acid near the middle of the second transmembrane segment of the β_2 or β_4 subunit of the nACh receptor. There are no data available for the molecular site of action of N_2O and Xe in the NMDA receptor. According to our results on the 5-HT₃ receptor, N_2O and Xe might act at the agonist recognition site for 5-HT rather than at the channel pore in the 5-HT₃

receptor. It is also possible that there might be multiple modulatory sites for these anesthetics in the agonist recognition domain of the 5-HT₃ receptor.^{4,5} Specific amino acid residues that seem to form part of the 5-HT binding site in the recombinant 5-HT₃ receptor have been identified as a glutamate residue²⁴ at 106 and tryptophan residues at 90, 183, and 195 in the N-terminal loops.²⁵ Further mutagenesis studies on these residues of the 5-HT₃ receptor will be required to reveal the detailed site of action for N₂O and Xe.

Recently, much interest has focused on the role of the 5-HT₃ receptor in PONV because specific 5-HT₃ receptor antagonists have been reported to clinically decrease the incidence of PONV.⁹⁻¹¹ These results suggest that anesthetics that inhibit the 5-HT₃ receptor might cause less PONV than those that substantially potentiate 5-HT₃ receptor function. In the current study, we showed that halothane and isoflurane potentiated the 5-HT₃ receptor but, surprisingly, that sevoflurane, N₂O, and Xe inhibited the 5-HT₃ receptor. According to clinical research about PONV after sevoflurane and isoflurane anesthesia, the incidence of PONV was lower in the sevoflurane group than in the isoflurane group.²⁶ Potentiation by halothane was much greater than that of isoflurane, consistent with a clinical study that showed the incidence of PONV after halothane anesthesia also to be greater than that of sevoflurane.²⁷ However, N₂O, which is thought to cause clinical emesis,²⁸ and Xe did not potentiate the 5-HT₃ receptor but rather inhibited it at clinical concentrations. Although little is known about the effects of Xe in terms of PONV, a study examining the analgesic potency of Xe reported nausea in 30% of volunteers.²⁹ Therefore, it is unlikely that all the effects of anesthetics on the 5-HT₃ receptor have an important role in producing PONV, although the potentiation of the 5-HT₃ receptor by halothane and isoflurane might be partly involved in the mechanism associated with their anesthesia. No clear conclusion is possible as to whether the effects of anesthetics on the 5-HT₃ receptor can be related to the clinical cause for PONV.

In this study, we showed volatile and gaseous anesthetics had diverse actions on the 5-HT₃ receptor. Both halothane and isoflurane were confirmed as enhancing homomeric 5-HT₃ receptor function in a concentration-dependent manner. In contrast, we revealed that sevoflurane inhibited the 5-HT₃ receptor noncompetitively, and N₂O and Xe inhibited the 5-HT₃ receptor competitively.

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