Effects of isoflurane and xenon on Ba\textsuperscript{2+}-currents mediated by N-type calcium channels

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Background. Isoflurane and xenon are inhalation general anaesthetics with differing clinical profiles and contrasting synaptic actions. Both agents have been shown to depress excitatory synaptic responses. Whether this is via pre-synaptic or post-synaptic mechanisms has not been determined clearly. N-type calcium channels are a putative pre-synaptic target for these agents. We tested whether N-type calcium channels were sensitive to isoflurane and xenon and whether there was any stereoselectivity in the effect of isoflurane.

Methods. We used patch-clamp electrophysiology on isolated HEK293 cells stably expressing N-type calcium channels to investigate the effects of isoflurane and xenon on barium currents mediated by N-type calcium channels.

Results. Racemic isoflurane caused a concentration-dependent reduction (11–35%) in the peak current through the N-type channels in the concentration range 0.15–1.22 mM. In the clinically relevant concentration range the inhibition was small. At an isoflurane concentration of 0.31 mM (equivalent to 1 MAC), the peak N-type current was inhibited by 14 (1)%. The optical isomers of isoflurane were found to be equally potent at inhibiting currents through N-type channels. The inert gas anaesthetic xenon was found to have no measurable effect on N-type channels at a concentration of 3.4 mM (∼1 MAC).

Conclusions. These results suggest that N-type calcium channels are not the targets mediating general anaesthesia with these two inhalation agents.

Br J Anaesth 2005; 94: 784–90

Keywords: anaesthetics volatile, isoflurane; electrophysiology; enantiomers; ion channel, Ca\textsuperscript{2+}; xenon

Accepted for publication: January 28, 2005

It has become almost axiomatic that general anaesthetics exert their actions at critical synapses in the CNS. However, the precise molecular target(s) underlying general anaesthesia are yet to be determined clearly. Particular attention has focused on the actions of anaesthetics on post-synaptic ligand-gated ion channels, including the GABAA receptor and the NMDA receptor. However, neuronal voltage-gated calcium channels also play an important role in signal transduction in the CNS, where they are involved in neurotransmitter release and regulation of neuronal excitability. Hence voltage-gated calcium channels are at least a plausible target for general anaesthetics.

Based on their pharmacology, electrical characteristics and genetic sequence homology voltage-gated calcium channels can be grouped into five classes, T (Ca\textsubscript{V} 3.1–3.3), L (Ca\textsubscript{V} 1.1–1.4), N (Ca\textsubscript{V} 2.2), P/Q (Ca\textsubscript{V} 2.1), and R (Ca\textsubscript{V} 2.3) types. T- and L-type channels are found in both neuronal and non-neuronal cells including heart and other muscle cells. On the other hand, N-, P/Q-, and R-type calcium channels have been found only in neurones and are involved in the release of neurotransmitter at synapses.\textsuperscript{1–3}

\textsuperscript{1}Declaration of interest. Professor Franks is a board member of an Imperial College spin-out company, Protexeon Ltd, that is interested in developing clinical applications for medical gases, including xenon. Professor Franks is a paid consultant in this activity. In addition Air Products have funded work in the authors’ laboratories that bears on the actions of xenon as an anaesthetic and neuroprotectant. Air Products has a financial stake in Protexeon Ltd.
Specific blockers of N-type calcium channels have been shown to inhibit both excitatory and inhibitory synaptic transmission in hippocampal neurones and antibody, aut radiographic, and epitope-tagging studies have localized N-type channels at pre-synaptic locations. Most of the studies of the effects of general anaesthetics on calcium channels have investigated T- and L-type channels, as a result in part to their involvement in cardiac function and to the easy accessibility of cells, particularly cardiomyocytes. Surprisingly, given their important role, there have been relatively few studies that have looked at the effects of anaesthetics on N-, P/Q-, and R-type calcium channels and these studies have often necessitated the use of ‘specific’ blockers to reveal the different currents in native tissue. In order to avoid the problems associated with pharmacological isolation of channels, we sought to investigate the effects of anaesthetics on defined N-type calcium channel subunits (α1B, α2δ, and β1b) in a stably expressing cell line. The auxiliary α2δ and β subunits modulate channel activity and are found in most calcium channels. We chose two very different inhalation agents, the volatile anaesthetic isoflurane and the inert gas xenon. Isoflurane has a chiral carbon atom and exists as two mirror image optical isomers (enantiomers), although it is used clinically as a racemic (equal) mixture of the isomers. In addition to the clinically used racemic isoflurane we also investigated the effects of the optical isomers of isoflurane.

Materials and methods

Cell culture

A stably expressing HEK 293 derived cell line expressing the N-type calcium channel subunits α1B, α2δ, and β1b from rat was a kind gift of SmithKline Beecham (Harlow, UK). Cells were cultured according to standard cell culture protocols in Dulbecco’s Modified Eagle’s Medium (Gibco, Invitrogen, Paisley, UK) containing 10% fetal bovine serum (Gibco), 100 units ml−1 penicillin (Gibco), 100 μg ml−1 streptomycin (Gibco), and 400 μg ml−1 gentamicin at 37°C and 5% CO2. The cells were passaged at confluence (usually weekly) and were used between passage numbers 6 and 18. Cells for use in electrophysiology were dissociated using non-enzymatic cell dissociation solution (Sigma, Poole, Dorset, UK) and plated on to glass cover slips coated with poly-d-lysine. These cells were grown at 28°C and 5% CO2 in the same medium as above. We found that expression of calcium channels was improved by maintaining the cells at 28°C. Cells were used for electrophysiology 2–3 days after plating.

Preparation of anaesthetic solutions

The anaesthetic solutions were prepared as described previously. Solutions of racemic isoflurane and its optical isomers were prepared in the same manner, as fractions of a saturated aqueous solution at room temperature. The concentration of saturated aqueous isoflurane solution was taken to be 15.3 mM. Racemic isoflurane was obtained from Abbott Laboratories (Queenborough, Kent, UK). The optical isomers of isoflurane were a gift from Anaquest Inc. (Murray Hill, NJ, USA). The purity of the isomers was determined using gas chromatography; the R(−) and S(+) isomers were found to have a chemical purity of 99.6 and 99.5%, respectively, and an optical purity of 99.4 and 100.0%, respectively. Solutions for the xenon experiments were prepared by bubbling oxygen, nitrogen or xenon through fine sintered-glass bubblers in Drechsel bottles containing extracellular saline. During the bubbling (~45 min) the solutions were stirred continuously at room temperature. The solutions were mixed to achieve the final desired concentrations of the gases. The test solutions contained xenon 80% and oxygen 20% while the control solutions contained nitrogen 80% and oxygen 20%. Using literature values for the Bunsen water–gas partition coefficient we calculated that the concentration of xenon in the test solution was 3.4 mM. We have shown previously using gas chromatography that losses of anaesthetic in our perfusion system are negligible.

Electrophysiology

Cells were voltage clamped (Axopatch 200 amplifier, Axon Instruments, Union City, CA, USA) using the whole cell recording technique. Electrodes were fabricated from borosilicate glass (GC150TF, Harvard Apparatus Ltd, Edenbridge, Kent, UK) and typically had resistances ~5 MΩ. Series resistance was compensated by at least 80%. Online leak subtraction was used with a P/4 protocol. Electrodes were filled with an intracellular solution containing (mM) 135 CsCl, 1 MgCl2, 10 HEPES, 14 creatine phosphate, 3.6 MgATP, 0.1 EGTA, 50 units ml−1 creatine phosphokinase, titrated to pH 7.1 with CsOH. The extra-cellular solution contained (mM) 143 tetraethylammonium (TEA)-Cl, 10 BaCl2, 1 MgCl2, 10 HEPES, 10 glucose, titrated to pH 7.4 with TEA-OH. Barium was used as the charge carrier as it gives larger currents than calcium and avoids calcium-induced current inactivation. Cells were clamped at a holding potential of −90 mV and currents were elicited by 50-ms depolarizing steps to holding potentials between −30 and +80 mV at a frequency of 0.25 Hz. (see Fig. 1A inset). The correction for liquid junction potential was calculated to be −10 mV using pClamp8 (Axon Instruments). Signals were filtered at 2 kHz using an 8-pole Bessel filter (model 900C, Frequency Devices, Inc., Haverhill, MA, USA), digitized at 5 kHz (Digidata 1200, Axon Instruments) and stored on a computer. Data were acquired and analysed offline using the pClamp software suite (Axon Instruments). Cells were pre-exposed to anaesthetic solutions for 1 min.
before eliciting currents. The run-down of control currents was variable, but typically ~15% over the course of an experiment. In order to correct for run-down of calcium channel currents the mean of the control current before and after exposure to anaesthetic was used to calculate the degree of inhibition. All results are quoted as mean (SEM).

Results

Control N-type currents

Currents were evoked by 50-ms depolarizing potential steps from a holding potential of −90 mV. Figure 1A shows typical N-type currents and the voltage protocol that elicited the currents shown. (C) Current–voltage relationship showing the peak current as a function of membrane potential. The currents have been normalized to the maximum current, elicited by a step to +20 mV. The data are from four cells. The errors bars are standard errors (SE) and where not shown these are smaller than the symbol. The curve is drawn by eye and has no theoretical significance.

Fig 1 (A) Typical currents elicited by a 50-ms step in membrane potential from a holding potential of −90 mV. The inset shows the voltage-step protocol that elicited the currents shown. (B) Current–voltage relationship showing the peak current as a function of membrane potential. The currents have been normalized to the maximum current, elicited by a step to +20 mV. The data are from four cells. The errors bars are standard errors (SE) and where not shown these are smaller than the symbol. The curve is drawn by eye and has no theoretical significance.

The enantiomers of isoflurane inhibit the peak current but do not affect the reversal potential. Current–voltage relationship in the absence (control) and presence of 0.6 mM of S(+)-isoflurane and R(−)-isoflurane. The currents have been normalized to the maximum control current, elicited by a step to +20 mV. The data are from four cells. The errors bars are SE and where not shown these are smaller than the symbol. The curves are drawn by eye and have no theoretical significance.

Fig 2 The enantiomers of isoflurane inhibit the peak current but do not affect the reversal potential. Current–voltage relationship in the absence (control) and presence of 0.6 mM of S(+)-isoflurane and R(−)-isoflurane. The currents have been normalized to the maximum control current, elicited by a step to +20 mV. The data are from four cells. The errors bars are SE and where not shown these are smaller than the symbol. The curves are drawn by eye and have no theoretical significance.

Fig 3 Inhibition of peak current, elicited by a step to +20 mV, as a function of racemic isoflurane concentration. The data shown are from a total of 18 cells. The errors bars are SE. The curve is drawn by eye and has no theoretical significance. The arrow indicates a concentration equivalent to 1 MAC. The inset shows a typical current trace in the absence and presence of 0.6 mM isoflurane.

Effect of racemic isoflurane on N-type currents

In the presence of isoflurane there was no change in threshold for current onset, potential for maximum current (+20 mV), or reversal potential (see Fig. 2). We therefore chose to measure the effects of anaesthetics on the peak of the maximum current, elicited at +20 mV (see Fig. 3 inset). The peak
of the N-type current elicited at +20 mV was reduced by racemic isoflurane in a concentration-dependent manner in the concentration range 0.15–1.22 mM, with inhibition ranging from 11 (2) to 35 (2)%, as shown in Figure 3. In the clinically relevant concentration range the degree of inhibition by isoflurane was small, being 14 (1)% at an isoflurane concentration of 0.31 mM, corresponding to 1 MAC.

**Effects of racemic isoflurane on the activation and inactivation curves for N-type currents**

We investigated the effects of isoflurane on the steady-state inactivation curve \( (h_{\text{inf}}) \) using a two-pulse protocol involving a 40 ms test pulse to +10 mV, from a holding level of −100 mV followed by a 2.5 s conditioning pre-pulse to different potentials followed by the second pulse to that elicited by the first test pulse. The results were fitted to a Boltzmann equation of the form

\[
h_{\text{inf}} = \frac{1 - C}{1 + \exp\left[\frac{V - V_0}{S}\right]} + C,
\]

where \( V \) is the membrane potential, \( V_0 \) is membrane potential at which current is 0.5 of maximum, \( S \) is the slope parameter and \( C \) is a constant. In the absence of isoflurane the value of \( h_{\text{inf}} \) was decreased in a depolarization-dependent manner with the value of \( V_0 = -60 \) (2) mV and \( S = 14 \) (1). In the presence of 0.6 mM isoflurane (−2 MAC) the inactivation curve was shifted in the hyperpolarized direction, as shown in Figure 4, with values of \( V_0 = -67 \) (1) mV and \( S = 12 \) (1). In contrast to the effect on the inactivation curve, the activation curve \( (m_{\text{inf}}) \) was unchanged in the presence of isoflurane with values of \( V_0 = 26 \) (1) mV and \( S = 17 \) (1) for the control curve and \( V_0 = 28 \) (1) mV and \( S = 17 \) (1) in the presence of 0.6 mM isoflurane, as shown in Figure 4.

**Effect of the optical isomers of isoflurane on N-type currents**

In order to investigate whether there was any stereoselectivity in the inhibition by isoflurane it was necessary to use a concentration in the clinical range, but that nevertheless gave enough inhibition to be able to make accurate measurements. Based on our measurements using racemic isoflurane we decided to use a concentration of 0.61 mM (corresponding to 2 MAC for the racemate) for our studies with the optical isomers. In the presence of either of the isomers there was no change in the reversal potential or potential for maximum current, as shown in Figure 2. In order to accurately determine whether there was any stereoselectivity and to control for cell-to-cell variation, we measured the inhibition by both the \( S(+) \)-isomer and the \( R(-) \)-isomer in a total of 12 cells. We found that there was no difference in the inhibition by the isomers, with 0.6 mM of the \( S(+) \)-isomer inhibiting the peak current by 22 (1)% while the same concentration of the \( R(-) \)-isomer inhibited by 23 (1)%, \( n = 12 \) cells.

**Effect of xenon on N-type currents**

The gaseous concentration of xenon for lack of response to a noxious stimulus is 71% in humans, 98% in monkeys, and 161% in rats. We have used previously these values together with the appropriate gas/water partition coefficients to calculate an average aqueous concentration corresponding to a MAC of 3.8 mM. In our experiments we used a standard test solution containing 3.4 mM xenon. We found that 3.4 mM xenon had no effect on the N-type currents at any potential tested. A typical current elicited at +20 mV in the absence and presence of the inert gaseous anaesthetic xenon is shown in Figure 5a. The I–V relationship was unchanged by 3.4 mM xenon as shown in Figure 5b.

**Discussion**

**Effects of isoflurane and its enantiomers on N-type currents**

Volatile anaesthetics have been shown to depress excitatory synapses and to potentiate inhibitory synapses. There has been controversy as to whether the observed depression of glutamatergic synapses by isoflurane is postsynaptic or pre-synaptic in origin, or a combination of both. A recent elegant study on glutamatergic responses at the Calyx of Held giant synapse has shown that clinical levels of isoflurane inhibit glutamate release. The authors attributed the majority of the inhibition to an effect on the pre-synaptic action potential; nevertheless there was a significant fraction that, while unaccounted for, appeared also to be pre-synaptic in origin. It remains to be seen whether these findings can be extended to other synapses in the CNS. However, it is apparent that pre-synaptic targets, to a greater

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**Fig 4** The effect of racemic isoflurane on the voltage-dependent activation \( (m_{\text{inf}}) \) and inactivation \( (h_{\text{inf}}) \) curves for N-type calcium channels. The inactivation curves have been normalized to the current at −90 mV. The activation curves have been normalized to the current at +80 mV. The filled circles are the control currents in the absence of isoflurane and the filled triangles are the currents in the presence of 0.6 mM racemic isoflurane. The error bars are \( \pm S \) for data from nine (activation) and seven cells (inactivation), respectively. The lines are fitted to a Boltzmann equation of the form

\[
m_{\text{inf}} = \frac{1 - C}{1 + \exp\left[\frac{V - V_0}{S}\right]} + C,
\]

where \( V \) is the membrane potential, \( V_0 \) is membrane potential at which current is half-maximum, \( S \) is the slope parameter and \( C \) is a constant.
or lesser degree, appear to be relevant to the reduction of glutamatergic responses by isoflurane. 

The voltage-gated calcium channels that are involved in triggering the release of neurotransmitter (N-, P/Q-, and R-type channels) are plausible pre-synaptic targets for isoflurane. P-type channels have been shown to be insensitive to isoflurane (and halothane), with concentrations equivalent to 1 MAC decreasing P-type currents by only 8%.23 R-type channels have been shown to be slightly more sensitive to volatile agents, although the inhibition is modest, with 0.35 mM isoflurane (~1 MAC) inhibiting peak currents by approximately 19% while 0.33 mM halothane inhibited peak currents by approximately 12%.24 The few studies that have looked at the effects of isoflurane on N-type channels have found the sensitivity to be modest (30–50% inhibition at concentrations corresponding to ~2.5 MAC)7,24 or variable.25 Nikonorov and colleagues studied the effects of isoflurane on pharmacologically isolated N-type currents in a human neuroblastoma cell line and found that the IC50 for inhibition by isoflurane varied from 0.3 to 0.7 mM depending on the level of G protein activation.

In order to avoid any ambiguity because of the use of ‘specific’ pharmacological blockers we set out to determine the sensitivity to isoflurane of defined N-type calcium channel subunits (α1B, α2/δ, and β1B) in a stably expressing cell line. Our finding that racemic isoflurane at a concentration of 0.31 mM (1 MAC) inhibited the current by 14 (1)%, is similar to the lack of sensitivity reported in other studies on N-type channels,7,24 although direct comparisons are complicated by the different systems used (Xenopus oocytes and DRG neurons) and by the lack of complete concentration–response curves. Our finding that isoflurane produces a leftward shift in the inactivation curve while not affecting the activation curve is qualitatively similar to findings by other workers.7 Quantitative differences with other studies may reflect the fact that we used barium as a charge carrier, which results in less inactivation of the current when calcium is used.

As a further test of the relevance of N-type channels as a putative target for isoflurane we looked at the effects of the enantiomers of isoflurane. The isoflurane enantiomers have different potencies in animals. The S(+)-isomer has a MAC value 50% greater than the R(−)-isomer in rats26 and the S(+)-isomer is 40% more potent at producing loss of righting reflex in rats,11 and induces 50% longer sleep time than the R(−)-isomer.11 If a particular target is relevant to these anaesthetic endpoints then the effects of the enantiomers should mirror the difference in whole-animal potency. We found that there was no difference in the inhibition of N-type currents by the isoflurane enantiomers, with the inhibition being 22 (1)% for the S(+)-isomer and 23 (1)% for the R(−)-isomer at a concentration of 0.6 mM. The lack of stereoselectivity at N-type calcium channels contrasts with the GABA_A receptor, which exhibits a stereoselectivity12 mirroring the difference in whole-animal potency.

**Effects of xenon on N-type currents**

Unlike isoflurane, and most other general anaesthetics, xenon appears to have little or no effect at GABAergic synapses, but it depresses glutamatergic synaptic responses.9,27 To our knowledge there have been no studies looking at the effects of xenon on N-type calcium channels (but see below for studies on L-type channels). We found that 3.4 mM xenon (a concentration equivalent to MAC) had no effect on N-type currents. Together with the fact that xenon’s depression of glutamatergic responses appears to be mediated by post-synaptic NMDA receptors,9,27 the lack of any effect on N-type calcium channels is consistent with the idea that xenon does not exert its anaesthetic effect through a pre-synaptic mechanism.

**Comparison with studies on L- and T-type calcium channels**

Considerable attention has focused on the effects of general anaesthetics on L- and T-type calcium channels (particularly...
L-type channels) in cardiomyocytes and smooth muscle cells of the airways, because effects on these channels may be related to adverse cardio-pulmonary side-effects of general anaesthetics.

Most studies that have looked at the effects of isoflurane on L-type calcium channels have found a lack of sensitivity similar to that which we observe in N-type channels (~14% inhibition at 0.31 mM isoflurane). A study on canine cardiac cells found that 0.29 mM isoflurane inhibited L-type channels by approximately 13% while another study found that 0.8 mM isoflurane inhibited currents by approximately 33%. A recent report using guinea pig cardiomyocytes has found different sensitivities to isoflurane of L-type channels in ventricular or atrial cells, with 0.3 mM isoflurane inhibiting the channels in the ventricular cells by only approximately 7% while those in the atrial cells were more sensitive, being inhibited by approximately 50% at the same concentration. The reason for the difference in sensitivity is not clear but it may reflect differences in channel subunits or regulatory proteins in the different cell types. Another confounding factor in comparing with other studies is the issue of experimental temperature and the temperature dependence of general anaesthesia. Ideally, when performing in vitro studies on mammalian ion-channels one would choose to work at 37°C, the temperature at which MAC values are determined. Unfortunately, for practical reasons this is not always possible and many studies (including this one) using in vitro preparations are performed at room temperature. In order for meaningful comparisons to be made it is important that the temperature dependence of the solubility of volatile anaesthetics is accounted for. Some studies have erroneously applied gas phase concentrations of anaesthetic appropriate at 37°C, to in vitro preparations at 20°C. As a result of the increased solubility of the anaesthetic at lower temperatures this results in significant overdosing of the preparation. For this reason we have expressed anaesthetic concentrations in the aqueous phase, which is much less affected by temperature changes and have limited comparisons with other studies to those where aqueous concentrations were measured or could be calculated from the relevant partition coefficients. A study using cells from bronchial muscle reported L- and T-type channels to be inhibited by approximately 16 and 25%, respectively, at a concentration of 0.25 mM isoflurane. Another study using recombinant T-type channels has reported 50% inhibition by 0.28 mM isoflurane. For isoflurane the overall picture that emerges is that voltage-gated calcium channels appear to be relatively insensitive at clinical concentrations.

With regard to the enantiomers of isoflurane we are not aware of other electrophysiological experiments on any type of calcium channel. However, a radio-ligand binding study on T-tubule membranes reported an IC50 of about 0.7 mM for racemic isoflurane in displacing the binding of a specific L-type channel ligand and found no difference between the isoflurane enantiomers. A similar lack of stereoselectivity of L-type channels was reported in an earlier binding study, although these authors used high concentrations of isoflurane. The lack of stereoselectivity of N-type channels contrasts with the difference in whole-animal potencies of the isoflurane enantiomers.

There has been a recent resurgence of interest in the use of xenon as a general anaesthetic (for a review see). As a result there have been some electrophysiological studies that have looked at the effects of xenon on L-type calcium channels in cardiomyocytes. Both of these studies found no significant effect of 1 MAC xenon on L-type currents. In addition a radio-ligand binding study found no effect of xenon on the binding of a specific ligand to L-type channels. The lack of any effect of xenon on L-type channels may explain why xenon appears not to depress the cardiovascular system. In conclusion, clinical concentrations of xenon have no significant effect on N- or L-type calcium channels.

Implications for general anaesthesia

We have shown previously that xenon inhibits glutamatergic synaptic responses by inhibiting the NMDA subtype of the glutamate receptor. The complete lack of effect of xenon on N-type calcium channels is consistent with the idea that the effects of xenon at glutamatergic synapses are entirely post-synaptic. Isoflurane on the other hand, appears to have a substantial pre-synaptic effect in addition to affecting post-synaptic receptors. The inhibition of N-type channels that we observe at clinical levels of isoflurane are small. Of course, it cannot be ruled out that the small inhibition by isoflurane of pre-synaptic N-type channels could be amplified (e.g. by a steep calcium dependence of transmitter release) to lead to a large reduction in neuronal function. However, if inhibition of N-type calcium channels were crucial to isoflurane anaesthesia then the prediction would be that the inhibition should be stereoselective. The fact that the isoflurane enantiomers are equally effective at N-type calcium channels, while differing in their whole-animal potencies, suggests that targets other than N-type calcium channels mediate isoflurane anaesthesia.

Acknowledgements

We thank John Akins and Ian Coole for technical assistance. This work was supported by the MRC, Carburos Metálicos SA, and Chelsea and Westminster Healthcare NHS Trust.

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