Influence of halothane and isoflurane on the contractile responses to potassium and prostaglandin F$_{2\alpha}$ in isolated human pial arteries

P. Reinstrup, T. Uski and K. Messeter

SUMMARY

Volatile anaesthetics may modulate cerebrovascular resistance, but their direct actions on human cerebral arteries are unknown. In the present study, we have evaluated the effects of halothane and isoflurane at different MAC (0.4, 1.0 and 2.0) on contractions induced by depolarization (potassium) or receptor stimulation (prostaglandin F$_{2\alpha}$) in isolated ring segments of human pial arteries. Neither halothane nor isoflurane had significant effects on potency (unaffected EC$_{50}$ value) or the maximum response (Emax) in potassium-contracted arteries, even though there was a general tendency to attenuation of Emax. Similarly, the potency of prostaglandin F$_{2\alpha}$ was unchanged (unaffected EC$_{50}$ value). However, the Emax value for prostaglandin F$_{2\alpha}$ at normocapnia (mean Pco$_{2}$ 4.3 (SEM 0.1) kPa, pH 7.41 (0.01)) and addition of halothane (0.4, 1.0 and 2.0 MAC) was significantly attenuated to 96 (2) %, 91 (3)% and 84 (4)% at the respective MAC concentrations. Isoflurane at 2 MAC and normocapnia also reduced Emax to 94 (3) %. During hypocapnia (Pco$_{2}$ 2.7 (0.1) kPa, pH 7.64 (0.01)), the vasodilator effect of halothane was reduced, whereas isoflurane at 0.4 and 1.0 MAC enhanced the contraction induced by prostaglandin F$_{2\alpha}$.

KEY WORDS


Halothane may increase cerebral blood flow (CBF), an effect which may be modulated by the ventilatory state of the patient [1]. Cortical CBF in humans increases less during isoflurane than during halothane anaesthesia [2, 3], suggesting that isoflurane dilates cerebral vessels to a lesser extent than halothane. Excessive cerebral vasodilation should be avoided in situations of compromised intracranial compliance, such as in patients with an intracranial mass lesion, in order to avoid causing an increase in intracranial pressure. Hence, the smaller dilator activity of isoflurane makes it preferable for anaesthesia during neurosurgical procedures.

The cerebrovascular dilatation produced by volatile anaesthetics may be caused by changes in neural innervation, it may be secondary to changes in the metabolism of the brain or it may result from a direct action on the cerebral arteries, or a combination of all three. Support for a direct action on the cerebral arteries has been presented by Harder and colleagues [4] who found that halothane directly relaxes feline cerebral arteries. However, there are no reports on the direct actions of volatile anaesthetics, during both normo- and hypocapnia, on human pial arteries.

We have compared the direct effects of halothane and isoflurane in depolarized or receptor-stimulated human pial arteries. The influence of these anaesthetics was evaluated also in arteries under hypocapnic conditions.

MATERIALS AND METHODS

Preparation

The experimental methods used in this study have been described previously [5]. Briefly, pial arteries were removed from macroscopically normal parts of brains in patients undergoing lobectomy because of underlying gliomas. The mean age of the patients in the halothane group was 42 (range 22-68) yr and in the isoflurane group 49 (40-68) yr. The age difference between the two groups was not statistically significant. None of the patients had a history of cardiovascular disease. Ring segments, 500-1000 μm in external diameter and approximately 2–3 mm long, were suspended between metal prongs in 5-ml organ baths containing physiological salt solution. Endothelium is preserved mainly with this technique [6]. One of the prongs was connected to a force transducer (grass Model FT 03C) for recording isometric tension and the output was displayed on a polygraph (Grass Model 7A). The ring segments were given a tension of 1 mN mm$^{-1}$ (length) and allowed to accommodate for 60–90 min. The contents of the organ baths were maintained at 37°C and equilibrated with a gas mixture (precision gas produced by Alfax, Malmö, Sweden) composed of 2.9 or 5.6% carbon dioxide and 30% oxygen in nitrogen. A Datex Normocap 102-24-02 (Datex, Finland) was used to constantly monitor the gas mixture. The partial pressures of carbon dioxide (Pco$_{2}$) and oxygen (Po$_{2}$) and the pH of the physiological salt solutions were analysed using a Radiometer (ABL 300, Radiometer, Denmark) (table I). A Tec 3 halothane or isoflurane vaporizer (Ohmeda, England) was serially connected to the

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fresh gas inlet and a gas analyser (Normac, Datex, Finland) was used to ensure that the correct percentage of volatile anaesthetics was delivered.

**Solutions and drugs**

The composition of the physiological salt solution was (mmol litre\(^{-1}\)): NaCl 119; NaHCO\(_3\) 20; KCl 4.6; CaCl\(_2\) 1.5; NaH\(_2\)PO\(_4\) 1.2; MgCl\(_2\) 1.3; glucose 11.0. Solutions containing different concentrations of K\(^+\) were obtained by exchanging NaCl in the physiological salt solution with equimolar amounts of KCl. PGF\(_2\alpha\) (Amoglandin, Astra, Sweden) was supplied as an aqueous solution and dilutions were made up with saline immediately before use. Volatile anaesthetics were added to the gas mixture used to equilibrate the bath content (see above) in concentrations corresponding to 0.4, 1 and 2 MAC (0.3, 0.7 and 1.4\% halothane and 0.5, 1.2 and 2.4\% isoflurane, respectively). The partition coefficient between physiological salt solution at 37 °C and air is 0.75 for halothane and 0.55 for isoflurane [7].

**Experimental procedure**

After an equilibration period with 95\% oxygen and 5\% carbon dioxide, contractions were induced between physiological salt solution at 37 °C and air is 0.75 for halothane and 0.55 for isoflurane [7].

| TABLE II. Effects of halothane (HAL) and isoflurane (ISO) at normo- and hypocapnia on contractions induced by excess K\(^+\). The contractions are characterized by the EC\(_{50}\) (mean), \(-\log (EC_{50})\) (mean (SEM)) and Emax (mean (SEM)) values. n = number of experiments. *P ≤ 0.05 |
|--------------------------|--------------------------|--------------------------|--------------------------|
| Experimental condition    | EC\(_{50}\) (mmol litre\(^{-1}\)) | \(-\log (EC_{50})\) | Emax (%) |
| Normocapnia-control       | 38.9                     | 1.41 (0.01)              | 100 (0)    |
| Normocapnia-0.4 MAC HAL   | 38.9                     | 1.41 (0.03)              | 99 (2)     |
| Normocapnia-1.0 MAC HAL   | 39.8                     | 1.40 (0.03)              | 98 (3)     |
| Normocapnia-2.0 MAC HAL   | 38.0                     | 1.42 (0.02)              | 96 (2)     |
| Hypocapnia-control        | 49.0                     | 1.31 (0.04)              | 100 (0)    |
| Hypocapnia-0.4 MAC HAL    | 50.1                     | 1.30 (0.05)              | 98 (7)     |
| Hypocapnia-1.0 MAC HAL    | 45.7                     | 1.34 (0.05)              | 92 (5)     |
| Hypocapnia-2.0 MAC HAL    | 47.9                     | 1.32 (0.06)              | 90 (4)*    |
| Normocapnia-control       | 42.7                     | 1.37 (0.04)              | 100 (0)    |
| Normocapnia-0.4 MAC ISO   | 39.8                     | 1.40 (0.02)              | 102 (2)    |
| Normocapnia-1.0 MAC ISO   | 40.7                     | 1.39 (0.03)              | 97 (3)     |
| Normocapnia-2.0 MAC ISO   | 38.9                     | 1.41 (0.02)              | 92 (3)     |
| Hypocapnia-control        | 50.1                     | 1.30 (0.05)              | 100 (0)    |
| Hypocapnia-0.4 MAC ISO    | 50.1                     | 1.30 (0.06)              | 98 (3)     |
| Hypocapnia-1.0 MAC ISO    | 51.3                     | 1.29 (0.06)              | 94 (3)     |
| Hypocapnia-2.0 MAC ISO    | 55.0                     | 1.28 (0.06)              | 96 (4)     |

**Calculations and statistical analysis**

The maximum response (Emax) in each preparation, obtained with either PGF\(_{2\alpha}\) or K\(^+\), under control conditions (30\% oxygen and either 5.6 or 2.9\% carbon dioxide) was defined as 100\%. All subsequent contractions in the presence of volatile anaesthetics were related to these responses. In the halothane group, the control Emax values induced by K\(^+\) and PGF\(_{2\alpha}\) were 8.34 (SEM 1.54) mN (n = 6) and 8.87 (1.59) mN (n = 6) at 5.6\% carbon dioxide and 9.15 (1.62) mN (n = 6) and 9.48 (1.44) mN (n = 6) at 2.9\% carbon dioxide. The control Emax values for the isoflurane group, induced by K\(^+\) and PGF\(_{2\alpha}\), were 6.37 (1.72) mN (n = 7) and 7.49 (1.69) mN (n = 7) at 5.6\% carbon dioxide and 6.92 (1.82) mN (n = 7) and 7.98 (1.65) mN (n = 7) at 2.9\% carbon dioxide. Estimation of the concentrations producing half maximum contraction (EC\(_{50}\)) for K\(^+\) and PGF\(_{2\alpha}\) was based on the geometrical means of the concentration–response curves. Curve fitting was performed with Graph Pad (ISI Software, Philadelphia, PA, U.S.A.) using the sigmoidal curve formula and assuming that the highest measured value corresponded to Emax. This constantly yielded correlation coefficients > 0.97 with PGF\(_{2\alpha}\) and > 0.95 with K\(^+\). The Wilcoxon rank sum test was used for determination of statistical significance between groups of Emax and EC\(_{50}\). P < 0.05 was accepted as significant.

**RESULTS**

Halothane or isoflurane did not affect the basal tone of unstimulated arteries.

**Effects of halothane and isoflurane on contractions induced by depolarization with potassium**

Stepwise depolarization of the smooth muscle membrane, attained with increasing concentrations

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**TABLE I. Mean (SEM) partial pressures of carbon dioxide and oxygen and pH in the physiological saline solution equilibrated with a normocapnic (3.6\% carbon dioxide) or hypocapnic (3.0\% carbon dioxide) gas mixture with 30\% oxygen in nitrogen**

<table>
<thead>
<tr>
<th></th>
<th>Po(_2) (kPa)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normocapnia</td>
<td>27.7 (0.2)</td>
<td>7.41 (0.01)</td>
</tr>
<tr>
<td>Hypocapnia</td>
<td>28.0 (0.2)</td>
<td>7.64 (0.01)</td>
</tr>
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</table>
of K⁺ at hypocapnia or normocapnia, induced concentration-dependent contractions. During normocapnia, neither isoflurane nor halothane significantly altered the Emax value, even if a slight tendency for depression of the contractions was detected. During hypocapnia, only 2.0 MAC of halothane had a significant effect on Emax. Neither of the two volatile anaesthetics altered the potency of K⁺, expressed by the EC₅₀ values. The Emax and EC₅₀ values during exposure to halothane or isoflurane are presented in Table II.

Effects of halothane and isoflurane on contractions induced by receptor stimulation with PGF₂α

Stepwise increments in receptor stimulation induced by increasing concentrations of PGF₂α at normo- or hypercapnia produced concentration-dependent contractions.

Halothane diminished the response to PGF₂α in a dose-dependent manner. During normocapnia, Emax was slightly but significantly reduced at 0.4 MAC (Fig. 1A). Hypocapnia diminished the vasodilator effect of halothane which differed significantly from control values only at 2.0 MAC (Fig. 1B), whereas the EC₅₀ values were unaffected. Emax and EC₅₀ values during exposure to halothane at normo- and hypocapnia are presented in Table III.

Isoflurane reduced the contractile response (Emax) during normocapnia in a dose-dependent manner. This attenuation of the contraction was significant compared with control contractions only at 2.0 MAC (Fig. 2A). In contrast, isoflurane at hypocapnia enhanced Emax, an effect which, however, was not significantly different from control at 2.0 MAC (Fig. 2B). Isoflurane did not modify the potency of PGF₂α at normocapnia or at hypocapnia, as the EC₅₀ value was unaffected (Table III).

The percentage change in maximal contraction (Emax) at normo- and hypocapnia at different concentrations of halothane and isoflurane are presented in figure 3.

DISCUSSION

We have found that halothane significantly attenuated vascular smooth muscle contraction in ring segments of isolated human pial arteries during receptor stimulation with PGF₂α. The same tendency was revealed in K⁺ depolarized arteries, although the relaxing effect was not significant. These findings are in accordance with reports from in vitro studies on cerebral arteries from the cat [4] and dog [9, 10]. Arteries of extracerebral origin, such as pig coronary [6], dog coronary [11, 12], rat coronary [13] and rat aorta [14], also react in a similar manner. Halothane depresses the metabolism of the brain [15], an effect which is believed to lower the demand of CBF. In spite of this, CBF increases in humans during exposure to halothane [2, 16] which supports the concept of a direct influence of halothane on cerebral vessels.

Addition of isoflurane attenuated the contractile response in human pial arteries during normocapnia. However, this effect appeared to be less than that observed during exposure to halothane. This finding is consistent with results from investigations on isolated canine cerebral arteries [10]. Also in humans, it is known that isoflurane has less pronounced dilator effects than halothane on the cerebrovascular bed in vivo [2, 3, 17]. Previously, this difference in the cerebral circulation was thought to result from the cerebral metabolic depression of isoflurane, which exceeds that of halothane [2, 18, 19]. Even if such an effect contributes to the action of isoflurane, our results suggest that the effects of the two anaesthetics also differ at the cerebrovascular level.

We observed a dose-dependent relationship between the attenuation of contraction and the concentration of halothane, which was most pronounced during normocapnia. In humans, CBF decreases with a lowering of PCO₂, the so-called carbon dioxide response [20, 21]. This effect probably reflects a direct action on the cerebral arteries, as lowering of
Table III. Effects of halothane (HAL) and isoflurane (ISO) at normo- and hypocapnia on contractions induced by PGF$_2$.
The contractions are characterized by the $EC_{50}$ (mean), $-\log (EC_{50})$ (mean (SEM)) and $Emax$ (mean (SEM)) values.

$n$ = number of experiments. *$P \leq 0.05$

<table>
<thead>
<tr>
<th>Experimental condition</th>
<th>$EC_{50}$ (mmol litre$^{-1}$)</th>
<th>$-\log (EC_{50})$</th>
<th>$Emax$ (%)</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normocapnia-control</td>
<td>1.51 x 10$^{-6}$</td>
<td>5.85 (0.15)</td>
<td>100 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Normocapnia-0.4 MAC HAL</td>
<td>1.45 x 10$^{-6}$</td>
<td>5.84 (0.16)</td>
<td>96 (2)*</td>
<td>6</td>
</tr>
<tr>
<td>Normocapnia-1.0 MAC HAL</td>
<td>1.62 x 10$^{-6}$</td>
<td>5.79 (0.16)</td>
<td>91 (3)*</td>
<td>6</td>
</tr>
<tr>
<td>Normocapnia-2.0 MAC HAL</td>
<td>1.99 x 10$^{-6}$</td>
<td>5.70 (0.16)</td>
<td>84 (4)*</td>
<td>6</td>
</tr>
<tr>
<td>Hypocapnia-control</td>
<td>1.20 x 10$^{-6}$</td>
<td>5.92 (0.14)</td>
<td>100 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Hypocapnia-0.4 MAC HAL</td>
<td>1.29 x 10$^{-6}$</td>
<td>5.89 (0.14)</td>
<td>99 (3)</td>
<td>6</td>
</tr>
<tr>
<td>Hypocapnia-1.0 MAC HAL</td>
<td>1.26 x 10$^{-6}$</td>
<td>5.90 (0.13)</td>
<td>96 (1)</td>
<td>6</td>
</tr>
<tr>
<td>Hypocapnia-2.0 MAC HAL</td>
<td>1.35 x 10$^{-6}$</td>
<td>5.87 (0.13)</td>
<td>96 (1)*</td>
<td>6</td>
</tr>
<tr>
<td>Normocapnia-control</td>
<td>2.63 x 10$^{-6}$</td>
<td>5.58 (0.13)</td>
<td>100 (0)</td>
<td>7</td>
</tr>
<tr>
<td>Normocapnia-0.4 MAC ISO</td>
<td>2.69 x 10$^{-6}$</td>
<td>5.57 (0.14)</td>
<td>98 (2)</td>
<td>7</td>
</tr>
<tr>
<td>Normocapnia-1.0 MAC ISO</td>
<td>2.88 x 10$^{-6}$</td>
<td>5.54 (0.13)</td>
<td>95 (3)</td>
<td>7</td>
</tr>
<tr>
<td>Normocapnia-2.0 MAC ISO</td>
<td>4.79 x 10$^{-6}$</td>
<td>5.32 (0.14)</td>
<td>94 (3)*</td>
<td>7</td>
</tr>
<tr>
<td>Hypocapnia-control</td>
<td>2.14 x 10$^{-6}$</td>
<td>5.67 (0.15)</td>
<td>100 (0)</td>
<td>7</td>
</tr>
<tr>
<td>Hypocapnia-0.4 MAC ISO</td>
<td>1.74 x 10$^{-6}$</td>
<td>5.76 (0.16)</td>
<td>105 (1)*</td>
<td>7</td>
</tr>
<tr>
<td>Hypocapnia-1.0 MAC ISO</td>
<td>2.19 x 10$^{-6}$</td>
<td>5.66 (0.16)</td>
<td>105 (1)*</td>
<td>7</td>
</tr>
<tr>
<td>Hypocapnia-2.0 MAC ISO</td>
<td>2.34 x 10$^{-6}$</td>
<td>5.63 (0.16)</td>
<td>104 (2)</td>
<td>7</td>
</tr>
</tbody>
</table>

FIG. 2. Effects of isoflurane 0.4 (△), 1.0 (○) and 2.0 (■) MAC on concentration–response curves obtained with PGF$_2$ at normocapnia (A) or hypocapnia (B). The contractions (mean, SEM) are expressed as percentage of maximum contraction obtained without isoflurane (control (●)) ($n = 7$).

$Pco_2$, with a concomitant change in pH, increased the maximal contraction to PGF$_2$ in isolated human pial arteries [22]. In the present study, the effects of $Pco_2$ are not included in the results, which thus reflect the action of the volatile anaesthetics, irrespective of the prevailing carbon dioxide tension. Previous investigations in humans have demonstrated that during halothane anaesthesia, the carbon dioxide response of the cerebral circulation is enhanced [15], which is consistent with a decrease in halothane-induced vasodepression during hypocapnia, as found in our study.

A seemingly novel finding from our experiments was that isoflurane enhanced the contractile response to PGF$_2$ during hypocapnia. However, a similar observation has been reported previously during partial depolarization of canine basilar and middle cerebral arteries [9], even though this finding is in contrast with our observation in K+-contracted human pial arteries. In vivo, Drummond and Todd [23] found that the carbon dioxide response in cats during administration of isoflurane was even more enhanced than with halothane. During isoflurane anaesthesia, hyperventilation is known to decrease cortical blood flow in cats [23] and rats [24] to a larger extent than during exposure to halothane. Cortical vasoconstriction may also account for the displacement of cerebral blood flow to more central regions as described in rats [25]. Even if lowering of $Pco_2$ did attenuate the depressant effect of halothane, we observed no reversal to enhanced contractility similar to the observation during isoflurane administration. In support of these findings, it was observed that addition of 1 MAC of halothane increased CBF in rabbits independent of the concentration of carbon dioxide, whereas isoflurane reduced CBF during hypocapnia and had no effect during normocapnia [26]. Thus even if the partly divergent results (probably reflecting species differences in the action of volatile anaesthetics) make comparisons between the different studies difficult, it seems evident that isoflurane may enhance, or at least preserve, the
INFLUENCE OF HALOTHANE AND ISOFLURANE ON PIAL ARTERIES

10

-10

-20

-10

-20

-10

-20

FIG. 3. Percentage change in maximal contraction (Emax) obtained with PGF2α at different concentrations of halothane (MAC) during normocapnia (A) and hypocapnia (B) or isoflurane during normocapnia (C) and hypocapnia (D). The contractions (mean, SEM) are expressed as percentage change in maximum contraction obtained without volatile anaesthetics. *Significantly different from control contractions (without volatile anaesthetics) (P < 0.05).

The cerebrovascular response to carbon dioxide more effectively than halothane.

The exact mechanism by which isoflurane and halothane modulate cerebrovascular tone is unknown. The present study was not designed to explore these mechanisms, but the differences in the responses of resting, depolarized and receptor-stimulated arteries imply some possible mechanisms. Halothane or isoflurane did not affect the basal tone of human pial arteries. A similar finding has been described with isoflurane in canine epicardial arteries [12]. These results indicate that the anaesthetics modulate only the active tone, suggesting an influence on, for example, sodium-potassium or calcium homeostasis in the smooth muscle cell [27]. However, the difference between the two anaesthetics cannot be explained by altered conformation of the receptor proteins, as no effect on the EC50 values (suggesting an unaltered affinity of PGF2α to its receptor) was found.

It has been shown that addition of halothane, and to some extent isoflurane also, results in hyperpolarization [28] which is believed to be secondary to an increase in potassium conductance of the cell membrane [29]. This provides an explanation for our observation of different effects of the two anaesthetics on PGF2α- and K+-contracted arteries. Relaxation induced by hyperpolarization is unattainable in K+-contracted arteries as the Na-K ATPase is activated maximally when the extracellular K+ concentration is increased to greater than the threshold for contraction [30]. Furthermore, an increase in extracellular K+ concentration blocks potassium channels [27].

Intracellular free calcium is a second messenger transducing different stimuli into contraction of the vascular smooth muscle cell. Plasma membrane depolarization leads to an influx of calcium which triggers the release of calcium from the sarcoplasmic reticulum [31]. Volatile anaesthetics interfere with calcium fluxes in the plasma membrane and in the membrane of the sarcoplasmic reticulum [32-34]. This mechanism may contribute to attenuation of contractions during addition of halothane and isoflurane. As mentioned above there was a difference in the effectiveness of the volatile anaesthetics in their
ability to relax arteries contracted by K⁺ or PGF₂α.
This may be a result of a greater effect of
the anaesthetics on receptor-mediated calcium influx
which occurs via routes other than the influx brought
about by depolarization [27].

In conclusion, the present study demonstrates that,
at normocapnia, halothane and isoflurane attenuated contractility in human pial arteries in a
dose-dependent manner. This attenuation of con-
traction was observed at hypocapnia also in arteries
exposed to halothane but changed to dose-inde-
pendent enhancement of the contraction in arteries
exposed to isoflurane.

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