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Isoflurane and Sevoflurane Induce Vasodilation of Cerebral Vessels via ATP-sensitive K^+ Channel Activation

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Background: **Activation of adenosine triphosphate–sensitive K^+ channels causes cerebral vasodilation. To assess their contribution to volatile anesthetic-induced cerebral vasodilation, the effects of glibenclamide, an adenosine triphosphate–sensitive K^+ channel blocker, on the cerebral vasodilation induced by isoflurane and sevoflurane were studied.**

Methods: **Pentobarbital-anesthetized dogs (n = 24) assigned to one of two groups were prepared for measurement of pial vessel diameter using a cranial window preparation. Each dog received three minimum alveolar concentrations (MAC; 0.5, 1, and 1.5 MAC) of either isoflurane or sevoflurane, and the pial arteriolar diameters were measured in the presence or absence of glibenclamide (10^{-5} M) infused continuously into the window. Mean arterial pressure was maintained with phenylephrine. Furthermore, to assess the direct effect of isoflurane and sevoflurane on cerebral vessels, artificial cerebrospinal fluid was administered topically by being bubbled with isoflurane or sevoflurane. The blocking effect of glibenclamide on the vasoactive effects of these anesthetics also were evaluated.**

Results: **Isoflurane and sevoflurane both significantly dilated large (≥ 100 μm) and small (< 100 μm) pial arterioles in a concentration-dependent manner (6% and 10%, 3% and 8% for 0.5 MAC; 10% and 19%, 7% and 14% for 1 MAC; 17% and 28%, 13% and 25% for 1.5 MAC). Glibenclamide attenuated the arteriolar dilation induced by these anesthetics (not significant in isoflurane). Topical application of isoflurane or sevoflurane dilated large and small arterioles both in a concentration-dependent manner. Such vasodilation was inhibited completely by glibenclamide.**

Conclusion: **The vasodilation of cerebral pial vessels induced by isoflurane and sevoflurane appears to be mediated, at least in part, *via* activation of adenosine triphosphate–sensitive K^+ channels. (Key words: Cerebral; glibenclamide; isoflurane; microcirculation; sevoflurane.)**

VOLATILE anesthetics exert significant vasodilator effects on various vascular beds. However, the effect of sevoflurane on cerebral vessels has not been established satisfactorily. This agent has been reported to decrease cerebral blood flow (CBF) in pigs,[1] not to affect CBF in rabbits and dogs,[2,3] and to increase CBF in rats.[4]

Although volatile anesthetics are potent vasodilators, the mechanism by which they relax vascular smooth muscle is not understood clearly. Many studies have shown that the membrane potential of the vascular smooth muscle cell is regulated mainly by the flow of Ca^{2+} and K^+ ions through specialized channels.[5–10] Adenosine triphosphate (ATP)-sensitive K^+ channels were first identified in cardiac muscle,[11] and more recently these channels also were found in vascular smooth muscle cells.[12] A recent report indicates that ATP-sensitive K^+ channels play an important role in the coronary vasodilation induced by volatile anesthetics.[13] We previously reported that ATP-sensitive K^+ channels are present in cerebral vessels in the dog, and that activation of these channels causes cerebral vasodilation.[14]

This study evaluated the comparative cerebral vasodilator effects of isoflurane and sevoflurane and assessed the contribution of ATP-sensitive K^+ channels to such cerebral vasodilation. We performed *in vivo* experiments using the cranial window technique during systemic and topical application of isoflurane or sevoflurane.

Materials and Methods

The experimental protocols were approved by our Institutional Committee for Animal Care, and the exper-

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iments were performed in 24 anesthetized dogs that weighed 6–10 kg. Anesthesia was induced with pentobarbital sodium (20 mg/kg administered intravenously) and maintained with a continuous infusion of pentobarbital sodium (2 $mg \cdot kg^{-1} \cdot h^{-1}$). After tracheal intubation, each dog was mechanically ventilated with oxygen-enriched room air and received pancuronium bromide (0.08 mg/kg) for muscle paralysis. The tidal volume and respiratory rate were adjusted to maintain an end-tidal carbon dioxide level of 35–40 mmHg. Polyvinyl chloride catheters were placed in the femoral vein and artery to administer drugs and fluids and to monitor blood pressure and collect blood samples. Rectal temperature was maintained between 36.5 and 37.5°C using a warming blanket.

A closed cranial window was used to observe the pial microcirculation. The animal was placed in the sphinx position, with the head immobilized in a stereotaxic frame. The scalp was retracted, the temporal muscle was removed, and a hole 2 cm in diameter was made in the parietal bone. After coagulation of the dural vessels with a bipolar electrocoagulator, the dura and arachnoid membrane were cut and retracted over the bone. A ring fitted with a cover glass was placed over the hole and secured with bone wax and dental acrylic. Four polyvinyl chloride catheters were inserted into the ring. The space under the window was filled with artificial cerebrospinal fluid (aCSF) composed of 151 mEq/l Na^+, 4 mEq/l K^+, 3 mEq/l Ca^{2+}, 110 mEq/l Cl^-, and 100 mg/dl glucose; *p*H was adjusted to 7.48, and the solution was bubbled with 5% carbon dioxide in air at 37°C. One catheter was attached to a reservoir bottle containing aCSF to maintain a constant intrawindow pressure of 5 mmHg. Two catheters were used to infuse and to drain aCSF and experimental drug solutions, and third one was used to continuously monitor intrawindow pressure. The volume below the window was between 0.5 and 1 ml.

All experiments were performed in the following manner. The animals were allowed to recover from the surgical procedures for at least 30 min. We confirmed the carbon dioxide reactivity of pial vessels prepared with the cranial window before and after experiments by comparing that information with our previous data[15] (in the hypercapnic condition [partial pressure of carbon dioxide in arterial blood, 55–60 mmHg], the diameter of pial arterioles were increased more than 5% compared with normocapnia; no animals were excluded in the current study).

Protocol 1

In the first set of experiments, aCSF was infused continuously at 1 ml/min into the cranial window in the control group (n = 12). To establish baseline values, pial arteriolar diameters, mean arterial pressure, heart rate, rectal temperature, arterial blood gas tensions, *p*H, blood glucose concentration, and serum electrolytes were measured (STAT Profile-5; NOVA Biomedicals, Waltham, MA) before the dogs received either isoflurane or sevoflurane (n = 6 for each agent). Dogs were assigned to receive three concentration of agents: 0.5, 1, and 1.5 minimum alveolar concentration (MAC) of either isoflurane or sevoflurane (end-tidal; M1025B, Hewlett Packard, Gentofte, Denmark) in a randomized manner (1.39% for 1 MAC and 2.36% for 1 MAC, respectively[16]; Isotec3 and Sevotec3 models, Ohmeda, Stteton, United Kingdom). The pial arteriolar diameters and the hemodynamic and physiologic variables, including rectal temperature, arterial blood gas tensions, *p*H, blood glucose concentration, and serum electrolytes, were measured again after a 15-min equilibration period during each dose of volatile anesthetic. We used a continuous infusion of phenylephrine to maintain a constant mean arterial pressure; this counteracted the decrease in mean arterial pressure associated with the administration of anesthetic agents. In the second set of experiments, we evaluated the effect of topical glibenclamide, an ATP-sensitive K^+ channel antagonist, on the vasodilator action of isoflurane or sevoflurane. Glibenclamide (10^{-5} M) in aCSF was infused continuously at a rate of 1 ml/min into the cranial window in this glibenclamide group (n = 12). The glibenclamide was dissolved in 100% dimethyl sulfoxide, and then diluted with aCSF. The final concentration of dimethyl sulfoxide in the glibenclamide solution actually used was 0.1%, which had no effect on vessels in the same model.[14] After baseline measurements had been taken, the dogs received isoflurane or sevoflurane in the same manner as the control group. All measurements, including pial arteriolar diameters, and hemodynamic and physiologic variables, were repeated, as in the control group.

Protocol 2

In additional experiments, to assess the direct effect of isoflurane and sevoflurane on cerebral vessels and the blocking effect of glibenclamide, we administered the solution into the window, which was bubbled in aCSF with the anesthetic (isoflurane or sevoflurane; 1.39% or 2.36% for 1 MAC solution, and 4.17% or 7.08% for 3 MAC solution) to the gas mixture of 5% carbon dioxide in air

Table 1. Hemodynamic and Physiologic Measurements

		MAP (mmHg)	HR (bpm)	*p*H	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	Na (mEq/l)	K (mEq/l)	BS (mg/dl)
Isoflurane									
Baseline	Control	124 ± 12	117 ± 15	7.43 ± 0.04	36 ± 4	200 ± 34	149 ± 3	4.4 ± 0.4	136 ± 29
	Glibenclamide	115 ± 14	138 ± 16	7.41 ± 0.05	35 ± 4	213 ± 25	147 ± 3	4.1 ± 0.3	134 ± 29
0.5 MAC	Control	125 ± 10	120 ± 15	7.42 ± 0.04	35 ± 4	198 ± 31	149 ± 2	4.3 ± 0.4	139 ± 22
	Glibenclamide	115 ± 14	133 ± 13	7.40 ± 0.05	37 ± 4	204 ± 29	147 ± 3	4.1 ± 0.4	125 ± 38
1.0 MAC	Control	127 ± 14	119 ± 19	7.41 ± 0.05	36 ± 3	191 ± 36	148 ± 3	4.2 ± 0.3	151 ± 19
	Glibenclamide	115 ± 14	128 ± 9	7.38 ± 0.05	38 ± 5	192 ± 37	146 ± 3	4.3 ± 0.4	139 ± 28
1.5 MAC	Control	127 ± 12	120 ± 19	7.38 ± 0.06	35 ± 3	182 ± 41	148 ± 3	4.5 ± 0.3	171 ± 28
	Glibenclamide	115 ± 12	134 ± 15	7.35 ± 0.06	39 ± 4	165 ± 33	145 ± 3	4.4 ± 0.3	149 ± 47
Sevoflurane									
Baseline	Control	121 ± 13	141 ± 25	7.41 ± 0.05	35 ± 2	192 ± 47	148 ± 3	4.0 ± 0.4	131 ± 9
	Glibenclamide	128 ± 10	140 ± 20	7.42 ± 0.02	37 ± 3	198 ± 21	149 ± 3	4.3 ± 0.4	118 ± 23
0.5 MAC	Control	122 ± 12	123 ± 21	7.41 ± 0.05	37 ± 2	188 ± 44	148 ± 2	4.2 ± 0.2	127 ± 32
	Glibenclamide	128 ± 10	130 ± 15	7.41 ± 0.01	37 ± 2	202 ± 31	149 ± 4	4.5 ± 0.2	118 ± 18
1.0 MAC	Control	122 ± 11	115 ± 23	7.39 ± 0.05	37 ± 4	180 ± 39	147 ± 1	4.4 ± 0.4	138 ± 24
	Glibenclamide	128 ± 12	127 ± 15	7.38 ± 0.03	40 ± 3	197 ± 32	148 ± 3	1.5 ± 0.2	140 ± 21
1.5 MAC	Control	123 ± 12	118 ± 18	7.38 ± 0.06	38 ± 5	170 ± 47	147 ± 2	4.2 ± 0.4	149 ± 27
	Glibenclamide	128 ± 11	124 ± 21	7.35 ± 0.04	40 ± 3	187 ± 30	148 ± 3	4.3 ± 0.2	165 ± 40

BS = blood sugar.

Values are mean ± SD (n = 6).

for 30 min at 37°C in each. Measurements were made, as in protocol 1, before and after topical administration of two concentrations of each solution into the window in 12 dogs (isoflurane, n = 6; sevoflurane, n = 6). To establish the baseline diameter of vessels, the window was continuously flushed with drug-free aCSF at 1 ml/min for 30 min after each measurement. After 30 min from the last administration of the study solution, the pial vascular diameter returned to baseline level. Furthermore, the concentration-dependent ability of glibenclamide (10^{-7} M and 10^{-5} M) to block the vasodilation induced by 3 MAC solution of isoflurane or sevoflurane was evaluated in each of the same six dogs in a randomized manner.

In each dog, the diameters of four pial arterioles (two of each were ≥ 100 μm and two of each were < 100 μm) were measured using a videomicrometer (Olympus Flovel videomicrometer, model VM-20; Flovel, Tokyo, Japan) attached to a microscope (model SZH-10; Olympus, Tokyo, Japan). The data from each pial view were stored on videotape for later analysis.

Statistical Analysis

All data relating to the concentration-dependent effects of the experimental drugs were tested using one-way analysis of variance for subsequent measurements and a paired Student's *t* test with a Bonferroni correction for *post hoc* comparisons. The data obtained during glibenclamide were compared with control values (aCSF infusion) with two-way analysis of variance followed by an unpaired Student's *t* test. In the additional experiments, two-way analysis of variance and an unpaired Student's *t* test were applied to compare large and small arterioles. The difference between the effects of isoflurane and sevoflurane was tested by two-way analysis of variance. Differences were considered significant at $P < 0.05$. All results are expressed as mean ± SD.

Results

Systemic Administration of Isoflurane or Sevoflurane (Protocol 1)

Mean blood pressure and heart rate did not vary significantly throughout the experiments, regardless of the concentration of isoflurane or sevoflurane or whether glibenclamide was used. In addition, arterial blood gas tensions and *p*H, serum electrolytes, and blood glucose concentration were not changed at any stage of the experiments (table 1).

Table 2 shows the baseline diameters of the pial vessels evaluated in the current study. There were no significant differences in baseline diameters of large or small vessels among the group (table 2).

Isoflurane and sevoflurane significantly dilated both large (≥ 100 μm) and small (< 100 μm) pial arterioles

Table 2. Baseline Diameter of Pial Vessels

	Large Arteriole (μm)	Small Arteriole (μm)
Isoflurane		
Control	142.7 ± 30.5	70.1 ± 10.8
Glibenclamide	130.9 ± 22.7	76.4 ± 10.1
Sevoflurane		
Control	147.2 ± 24.4	70.8 ± 10.5
Glibenclamide	146.7 ± 46.4	75.3 ± 9.2

Values are mean ± SD.

in a concentration-dependent manner (6% and 10%, 3% and 8% for 0.5 MAC; 10% and 19%, 7% and 14% for 1 MAC; 17% and 28%, 13% and 25% for 1.5 MAC, respectively). There was no difference between isoflurane and sevoflurane in terms of the dilation of pial arterioles induced by any given concentration. For each agent, the dilation was more prominent in small arterioles than in large ones (fig. 1). Glibenclamide tended to attenuate such vasodilations in isoflurane (not significant), and significantly attenuated them at all concentrations in large and small arterioles in sevoflurane, although the infusion of glibenclamide into the cranial window did not itself affect pial vascular diameters (1.7 ± 5.1% in large and 0.3 ± 5.4% in small arterioles; difference not significant).

Topical Administration of Isoflurane or Sevoflurane (Protocol 2)

In a preliminary experiment, we measured the concentration of isoflurane or sevoflurane in aCSF bubbled with isoflurane and sevoflurane by gas chromatography (0.28 ± 0.03 mM for 1 MAC; 0.84 ± 0.07 mM for 3 MAC in isoflurane, and 0.23 ± 0.03 mM for 1 MAC; 0.70 ± 0.09 mM for 3 MAC in sevoflurane). Topical application of isoflurane and sevoflurane bubbled in aCSF significantly dilated large and small pial arterioles in a concentration-dependent manner. There was no difference between the degree of vasodilation in large and small arterioles induced by isoflurane and sevoflurane. Both 10^{-7} M and 10^{-5} M glibenclamide completely blocked the dilation induced by 3 MAC isoflurane or sevoflurane (fig. 2).

Mean arterial pressure and heart rate did not change significantly before and after topical application of any tested solution. In addition, arterial blood gas tensions and *p*H, serum electrolytes, and blood glucose concentration were not changed at any stage of the experiments.

Discussion

The primary findings of this study were that (1) inhalation of either isoflurane or sevoflurane induces vasodilation of cerebral pial arterioles in a similar concentration-dependent manner, and glibenclamide attenuates the arteriolar dilation induced by these anesthetics (not significant in isoflurane), and (2) topical application of either isoflurane and sevoflurane induces a vasodilation of cerebral pial arterioles in a concentration-dependent manner, and glibenclamide blocked the arteriolar dilation induced by these anesthetics completely. Therefore, the cerebral vasodilation appears to be, at least in part, caused by activation of ATP-sensitive K^+ channels.

We previously reported that ATP-sensitive K^+ channels are located in cerebral vessels in the dog, that their activation causes cerebral vasodilation, and that topical administration of glibenclamide inhibits this vasodilation.[14] Other reports also suggest that ATP-sensitive K^+ channels can contribute to the regulation of the cerebral circulation in various situations.[17,18] In the current study, topical infusion of glibenclamide attenuated the cerebral vasodilation induced by inhaled isoflurane and sevoflurane, and it blocked completely the cerebral vasodilation induced by topical administration of isoflurane and sevoflurane. However, the current data do not permit us to identify the mechanisms by which ATP-sensitive K^+ channels were activated by the volatile anesthetics used. It may involve a direct action, or be secondary to a reduction in ATP in cerebral smooth muscle, prostacyclin release,[19] adenosine receptor activation,[12] or interaction with phosphorylation enzymes.[20] Whatever the underlying mechanism, our results suggest that an activation of ATP-sensitive K^+ channels by isoflurane and sevoflurane is at least partly responsible for the cerebral vasodilation induced by these agents. Because there were differences in vascular responses between systemic (attenuated response) and topical (completely blocked response) administration of these anesthetics, vasodilation induced by inhaled isoflurane or sevoflurane may be mediated, in part, with mechanisms other than ATP-sensitive K^+ channel activation.

The mechanism underlying the cerebral vasodilation induced by volatile anesthetics is not well understood. Several mechanisms involving modulation of intracellular communication have been proposed, including direct effects on ion channels[21–25] and indirect effects *via* nitric oxide[26–28] and prostanoids.[29] The membrane potential of vascular smooth muscle is regulated mainly by the flow of Ca^{2+} and K^+ ions through specialized chan-

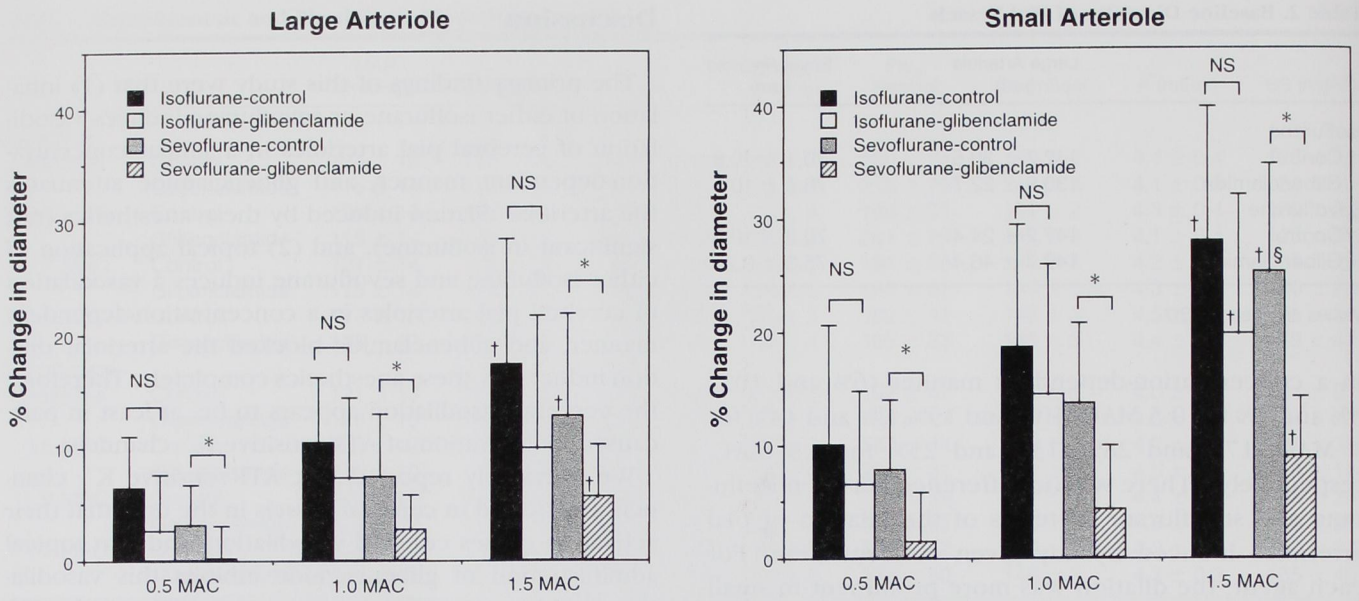

Fig. 1. The concentration-related effects of inhaled isoflurane and sevoflurane on the diameters of pial arterioles (large arteriole [≥ 100 μm]; small arteriole [< 100 μm]) in 24 dogs. Data are expressed as percentage changes in diameter. Isoflurane and sevoflurane significantly dilated both large and small pial arterioles in a concentration-dependent manner. Glibenclamide attenuated such vasodilations (difference not significant in isoflurane). Values are expressed as mean ± SD (n = 12 for each column). *P < 0.05 for comparisons between indicated values. NS = not significant. †P < 0.05 compared with the corresponding 0.5 minimum alveolar concentration value. §P < 0.05 compared with the corresponding 1 minimum alveolar concentration value.

nels. In general, the contractile mechanisms in cerebral vessels seem to be more dependent on the influx of extracellular Ca^{2+} than on the movement of Ca^{2+} out of the intracellular store.[12] Activation of K^+ channels in the cerebral circulation could cause a membrane hyperpolarization that would reduce the influx of Ca^{2+} through voltage-dependent Ca^{2+} channels and induce vascular relaxation.[30] However, Marijic *et al.*[24] found that blockade of Ca^{2+}-activated K^+ channels with tetraethylammonium chloride actually potentiates the vasorelaxing effects of volatile anesthetics. Furthermore, several reports indicated that volatile anesthetics inhibit Ca^{2+}-activated K^+ channels in various cells.[21–23] In addition, Eskinder *et al.*[24] showed that the cerebral vasodilation induced by volatile anesthetics is not mediated through modulation of Ca^{2+}-activated K^+ channels in cerebral vessels because no significant effect was produced by tetraethylammonium chloride. From the results of these studies, it would appear that activation of Ca^{2+}-activated K^+ channels is unlikely to be the main mechanism responsible for the cerebral vasodilation induced by isoflurane and sevoflurane.

We previously reported that topical application of 10^{-5} M glibenclamide inhibited the dilation of arterioles induced by cromakalim and nicorandil, ATP-sensitive K^+ channels openers, but not by nitroglycerin in the same model.[14] Although we tried to assess the concentration-dependent effect of topical glibenclamide in protocol 2, we could not observe any difference in the inhibiting effect between 10^{-7} M and 10^{-5} M glibenclamide. Therefore, it is suggested that the concentration of glibenclamide used in the current study appears to be optimal. Because the basal anesthetic state with pentobarbital might affect the cerebrovascular tone in arterioles and because there are no data about how pentobarbital, although least effective on cerebrovascular tone in isolated dog experiments,[31] affects the vascular effect *via* ATP-sensitive K^+ channels, we cannot exclude the possibility that the effects we observed on pial vessel tone during isoflurane and sevoflurane anesthesia could be mediated, at least in part, by the presence of pentobarbital. In addition, the interaction of phenylephrine used to maintain blood pressure during inhalation of isoflurane or sevoflurane in the current study might influence the effect of volatile anesthetics on cerebral vasodilation *via* potassium channel activation. This might be responsible for the difference in the antagonistic effect of glibenclamide between isoflurane and sevoflurane inhalation (difference not significant in isoflurane).

Published data regarding the effects of sevoflurane on cerebral circulation are inconclusive. Sevoflurane, in contrast to isoflurane, has been reported to decrease

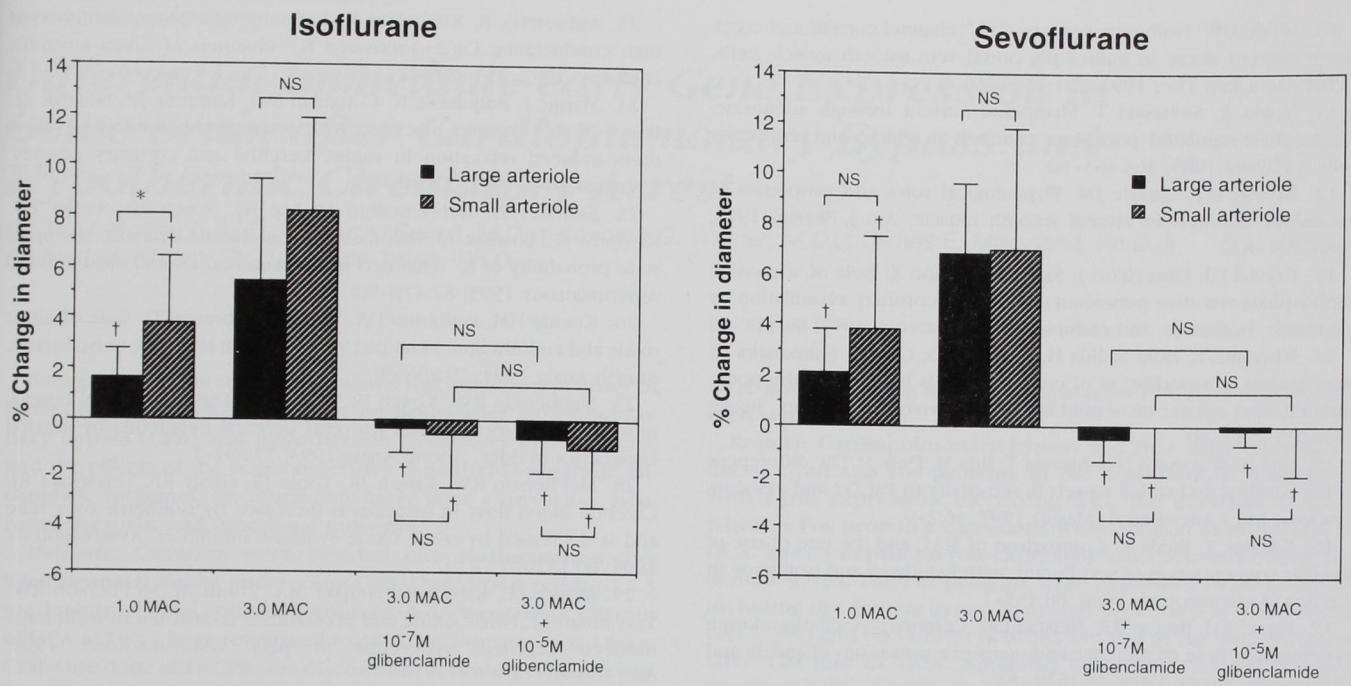

Fig. 2. The concentration-related effects of the topical application in isoflurane and sevoflurane on the diameter of pial arterioles (large arterioles [≥ 100 μm]; small arterioles [< 100 μm]) in 12 dogs. Data are expressed as percentage changes in diameter. Isoflurane and sevoflurane dilated both large and small pial arterioles. Both 10^{-7} M and 10^{-5} M glibenclamide blocked the vasodilation induced by topical 3 minimum alveolar concentration sevoflurane and isoflurane completely. Values are expressed as mean ± SD (n = 12 for each column). *$P < 0.05$ for comparison between indicated values. NS = not significant. †$P < 0.05$ compared with the corresponding 3 minimum alveolar concentration value.

CBF in pigs[1], not to affect CBF in rabbits and dogs,[2,3] and to increase CBF in the same manner as isoflurane in rats.[4] In the current study, we found that isoflurane and sevoflurane both significantly dilated large and small pial arterioles in a concentration-dependent manner, with the extent of the effects about the same for sevoflurane and isoflurane at any particular concentration. Although a species difference is also apparent among the various studies,[1-4,32,33] vasodilation in arterioles is likely to be induced to a similar degree by sevoflurane and isoflurane anesthesia as a result of systemic topical application of these anesthetics, as in the current study.

In conclusion, the vasodilation of cerebral pial vessels induced by isoflurane and sevoflurane appears to be mediated, at least in part, by activation of ATP-sensitive K^+ channels. The effects of sevoflurane on cerebral arterioles are similar to those of isoflurane, an agent that is accepted widely as an anesthetic for neurosurgical procedures.

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