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Region-specific and Agent-specific Dilation of Intracerebral Microvessels by Volatile Anesthetics in Rat Brain Slices

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Background: **Volatile anesthetics are potent cerebral vasodilators. Although the predominant site of cerebrovascular resistance is attributed to intracerebral arterioles, no studies have compared the actions of volatile anesthetics on intraparenchymal microvessels. The authors compared the effects of halothane and isoflurane on intracerebral arteriolar responsiveness in hippocampal and neocortical microvessels using a brain slice preparation.**

Method: **After Institutional Review Board approval, hippocampal or neocortical brain slices were prepared from anesthetized Sprague-Dawley rats and placed in a perfusion–recording chamber, superfused with artificial cerebrospinal fluid. Arteriolar diameters were monitored with videomicroscopy before, during, and after halothane or isoflurane were equilibrated in the perfusate. $PGF_{2\alpha}$ preconstricted vessels before anesthetic administration. A blinded observer using a computerized videomicrometer analyzed diameter changes.**

Results: **Baseline microvessel diameter and the degree of preconstriction were not different between groups. In the hippocampus, the volatile agents produced similar, concentration-dependent dilation (expressed as percent of preconstricted control ± SEM) of 68 ± 6% and 79 ± 9% (1 MAC) and 120 ± 3% and 109 ± 5% (2 MAC) ($P < 0.05$) during halothane and isoflurane, respectively. In the cerebral cortex, isoflurane caused significantly less vasodilation than did similar MAC levels of halothane (84 ± 9% *vs.* 42 ± 5% dilation at 1 MAC; 121 ± 4% *vs.* 83 ± 5% dilation at 2 MAC halothane *vs.* isoflurane, respectively).**

Conclusion: **Halothane and isoflurane differentially produce dose-dependent dilation of intraparenchymal cerebral microvessels. These findings suggest that local effects of the volatile anesthetics on intracerebral microvessel diameter contribute significantly to alterations in cerebrovascular resistance and support previously described heterogeneous actions on cerebral blood flow produced by these agents. (Key words: Anesthetics, volatile: halothane; isoflurane. Brain: brain slices; hippocampus; neocortex. Cerebral arterioles: vasodilation; microvessel.)**

VOLATILE anesthetics are well-known cerebral arterial vasodilators[1,2] and increase cerebral blood flow (CBF) in many experimental preparations. Halothane and isoflurane relax cerebral arteries *in vivo*[1-3] and in isolated vessel preparations.[4-6] It is generally believed that halothane causes greater increases in CBF than does isoflurane, and thus halothane has potentially greater deleterious effects on intracranial pressure.[1,2] However, recent studies suggest that the effects of volatile anesthetics on regional CBF are heterogeneous despite an essentially uniform depression of regional cerebral metabolism for glucose (CMRGlu) and similar effects on global CBF.[7,8] The net effect of volatile anesthetics on CBF depends on the balance between a direct vasodilatory action and an indirect vasoconstrictive response resulting from metabolic depression.[2,3,8,9] During maximal metabolic suppression, isoflurane produces greater increases in cerebrocortical flow than did halothane.[9,10] Isoflurane may cause preferential dilation of small cerebral vessels as compared with those dilated by halothane.[11] In addition, isoflurane redistributes CBF to sub-

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cortical regions, as determined by ^{14}C-iodoantipyrine autoradiography[7] or single photon emission computer-aided tomography.[12] Volatile anesthetic effects on pial microvessels and regional cerebral perfusion with the use of a closed cranial window[10,13] have provided valuable information, although the preparations are limited to either superficial blood vessels or regional blood flow rather than to specific actions of the anesthetics at the intraparenchymal arteriolar level. This investigation uses an *in vitro* brain slice preparation[14-16] to examine the hypothesis that differences in the hyperemic effect of various volatile anesthetics in specific brain regions are a result of varying degrees of vasodilation of intraparenchymal microvessels that directly regulate capillary perfusion and are the predominant site of cerebrovascular resistance.[17,18] We have recently demonstrated that halothane potently and dose-dependently dilates hippocampal microvessels in this preparation.[19] The purpose of this study was to compare microvascular responsiveness to halothane *versus* isoflurane in two distinct brain regions, the hippocampus and the cerebral neocortex.

Methods

All experimental procedures and protocols used in this investigation were reviewed and approved by the Animal Use and Care Committee of the Medical College of Wisconsin. Protocols were completed in accordance with the Guiding Principles in the Care and Use of Laboratory Animals of the American Physiological Society and in accordance with National Institutes of Health guidelines.

General Preparation

Adult male Sprague-Dawley rats (250-350 g body weight, with no significant weight differences between animals in each group) were anesthetized in a specially designed holding chamber by breathing 2% volatilized halothane (Anaquest Inc., Madison, WI) in 100% oxygen. A midline thoracotomy was performed, and 20 ml of buffered saline was infused intracardially into the left ventricle while a right atrial incision was simultaneously made for blood drainage. The animals were then decapitated, and the brains were rapidly removed and rinsed with nutrient medium (artificial cerebrospinal fluid [aCSF]) of the following composition (mM): NaCl, 124; KCl, 5; $CaCl_2$, 2.4; $MgCl_2$, 1.3; glucose, 10; KH_2PO_4, 1.24; $NaHCO_3$, 26; gaseous equilibration with 95% O_2 and 5% CO_2; pH, 7.4. Nutrient medium was prepared daily, and all measurements of cerebral microvessel diameters were performed on the same day as the tissue slices were prepared.

Brains were cut freehand into blocks containing the hippocampus and somatosensory neocortex, followed by immediate sectioning into coronally oriented tissue slices (250-280-μm thick; at coordinates 2.6-4.2 mm posterior to bregma[20]), with a vibratome mechanical tissue slicer (OTS-3000-03, FHC, Brunswick, ME). Throughout the slicing procedure, tissues were continuously bathed in the oxygenated aCSF at or slightly below room temperature. Subsequently, the slices were transferred to a plexiglass holding chamber and maintained at interface with oxygenated aCSF. Individual slices were then transferred for examination to a recording chamber mounted on an inverted halogen transillumination microscope (Nikon Diaphot 200, Yokohama, Japan).

The recording chamber was designed in this laboratory and consisted of a center recording-superfusion compartment of 2.8 ml. Slices were submerged onto a nylon mesh, allowing continuous superfusion of aCSF under and around the brain slices, with flow through the recording chamber at a rate of 1.5 ml/min. The chamber temperature was continuously monitored and maintained at 34°C using a thermoelectric Peltier heating device coupled to a sensing thermistor. The slices were maintained in this chamber, continuously superfused with the oxygenated aCSF for approximately 1 h before the initiation of the experimental protocol.

Microscopy

An intraparenchymal arteriole (10-30 μm in diameter) was located within the neuronal tissue, and its diameter was continuously monitored with videomicroscopy. Videomicroscopy equipment consisted of an inverted halogen transillumination microscope, a 40 $\times$ objective (Olympus WPlanFL 160/0, Tokyo, Japan), and a 2.25 $\times$ video projection lens (Nikon CCTV/Microscope Adapter, Yokohama, Japan). Arterioles were microscopically identified and differentiated from venules by the presence and characteristics of the vascular smooth muscle. The image was then transmitted to a video camera (CCD 72, Dage MTI, Michigan City, IN) and displayed on a video monitor (Sony HR Trinitron, Tokyo, Japan). Vessel diameter changes were recorded on videotape using a VHS video recorder (Magnavox, Rebersburg, PA) and analyzed using a video micrometer and computerized imaging analysis (Metamorph Im-

Table 1. Baseline Measurements of Microvessel Diameters and aCSF Gases

Parameter	Halothane		Isoflurane	
	Hippocampus	Neocortex	Hippocampus	Neocortex
Diameter (μm) [range (mean ± SEM)]	9–39 (18 ± 2)	11–31 (18 ± 2)	9–39 (14 ± 2)	10–33 (16 ± 2)
Preconstriction (%)	14 ± 1	14 ± 1	14 ± 1	14 ± 1
*p*H	7.37 ± 0.02	7.41 ± 0.01	7.35 ± 0.02	7.39 ± 0.02
P_{CO_2}	39 ± 2	36 ± 2	41 ± 2	37 ± 1
P_{O_2}	225 ± 20	230 ± 10	242 ± 24	233 ± 10

Values are mean ± SEM. There are no significant differences between groups.

aging System, Universal Imaging Corp., West Chester, PA) using an IBM-compatible computer. Intraluminal diameter of cerebral microvessels was measured on-line and off-line using this computerized measuring system with sensitivity to 0.1 μm.

An intracerebral microvessel was located, and baseline luminal diameter measurements were obtained after the 60-min equilibration period. The aCSF that superfused the brain slices was aerated with a mixture of oxygen, carbon dioxide, and air sufficient to maintain the pH and P_{CO2} within normal limits and the P_{O2} at 220 ± 20 mmHg (table 1). Gas analysis of the superfused fluid was performed at baseline and every 60 min throughout the experimental period using a blood gas analyzer (Radiometer ABL 3, Copenhagen, Denmark).

Experimental Protocol

After baseline diameter measurements, $PGF_{2\alpha}$, dissolved in aCSF to a concentration of 500 nM, was superfused over the slice for 30 min. Once a stable preconstricted (control) diameter was established, intraluminal diameter measurements were again obtained and recorded, and either halothane or isoflurane was administered during the continuous $PGF_{2\alpha}$ superfusion. Halothane or isoflurane was delivered to the slices by volatilizing the anesthetic agents into the aCSF by passing the oxygen, carbon dioxide, and air mixture through vaporizers (Model F100, Ohio Medical Products; Airco Inc., Madison, WI). Halothane or isoflurane was administered in a graded concentration fashion, in which each slice was exposed to at least three concentrations of volatile anesthetic. The vaporizer dial settings used were 0.5%, 1%, 1.5%, 2%, 3%, and 5%. After introduction of the volatile anesthetic or any change in concentration, 30 min was allowed for equilibration. After volatile anesthetic equilibration, microvessel diameter was again measured and recorded.

In two separate groups of brain slices, experiments were performed to determine the specific effect of preconstriction on microvascular responsiveness to isoflurane. 1 MAC and 2 MAC concentrations of isoflurane were administered to hippocampal brain slices, as described previously, in the presence (n = 6) and absence (n = 9) of preconstriction with $PGF_{2\alpha}$ (500 nM). In these experiments only, the percent dilation was calculated by dividing the maximum diameter after dilation by the baseline (nonpreconstricted) diameter to avoid biasing calculations in the absence of preconstriction.

Data Analysis

The average microvessel diameters were derived as an average of 8–13 measurements taken every 6–10 μm along an average of 80 μm of vessel length. The amount of microvessel constriction after $PGF_{2\alpha}$ was calculated using the following equation: $(D_{BL} - D_{PGF})/D_{BL}$; where D_{BL} represents the baseline, resting diameter of the microvessel, and D_{PGF} represents the control diameter of the microvessel after administration of $PGF_{2\alpha}$. The amount of arteriolar dilation caused by the volatile anesthetics halothane or isoflurane was normalized to the amount of constriction produced by $PGF_{2\alpha}$ and was calculated using the following equations: $(D_{VA} - D_{PFG})/(D_{BL} - D_{PGF})$; where D_{VA} is the diameter of the microvessel after administration of the particular anesthetic used. Brain slices were excluded from analysis if microvessels could not be adequately visualized or if the luminal diameter of the microvessels were not clearly discernible throughout the experiment.

Artificial CSF fluid samples were obtained from the superfusate during each vessel diameter measurement, with the halothane and isoflurane concentrations subsequently measured using gas chromatography (Sigma 3B, Perkin-Elmer, Norwalk, CT). The millimolar concentra-

tions of each volatile anesthetic measured in the bath were then converted to equivalent partial pressures in the solution, calculated as a percentage of the volatile agent in the gas phase,[21] and expressed as MAC values (1 MAC: isoflurane, 1.4%; halothane, 1.1%). The MAC values chosen are commonly accepted for rats and are consistent with those obtained in our laboratory. The reported volatile anesthetic levels are those calculated from the measured concentrations and not the vaporizer dial settings.

Statistical Analysis

Microvessel diameter changes measured in a series of experiments were averaged for each anesthetic concentration. All raw and normalized data were analyzed by two-way repeated measures analysis of variance (ANOVA) to compare differences within and between groups at multiple anesthetic concentrations. Pairwise comparisons of interventions were performed with contrasts derived from the repeated measures analysis and adjusted for multiplicity by Duncan's modification of the *t* test. Changes in vessel diameter at each concentration of halothane or isoflurane were compared with the microvessel diameter during $PGF_{2\alpha}$ preconstriction (control) and between anesthetic agents at equi-MAC concentrations. Differences were considered statistically significant when the *P* value is less than 0.05. All data were expressed as mean ± SEM.

Results

One hundred two brain slices were obtained from 75 animals. There was not more than one slice per animal used for an experiment. Twenty-five brain slices completed the protocol with halothane (14 hippocampal, 11 neocortical), and 26 slices completed the protocol with isoflurane (13 hippocampal, 13 neocortical). An additional 16 brain slices from 13 animals were used to determine the influence of preconstriction on isoflurane-induced changes in vessel responsiveness. Baseline microvessel diameters were not different between the groups. Administration of the $PGF_{2\alpha}$ infusion resulted in a stable cerebral microvessel constriction of 14% from baseline, resting diameter, in all four groups (table 1). This amount of constriction was used to normalize the percent dilation produced by either halothane or isoflurane.

In preliminary experiments, it was determined that even in the absence of $PGF_{2\alpha}$-induced preconstriction, significant intraparenchymal microvessel dilation occurred during isoflurane. However, the degree of isoflurane-mediated vasodilation was significantly less (7% and 12% dilation from resting diameter at 1.0 and 2.0 MAC, respectively), in the absence of preconstriction, than was the response to isoflurane in preconstricted vessels (14% and 19% dilation from preconstricted diameter at 1.0 and 2.0 MAC, respectively; fig. 1).

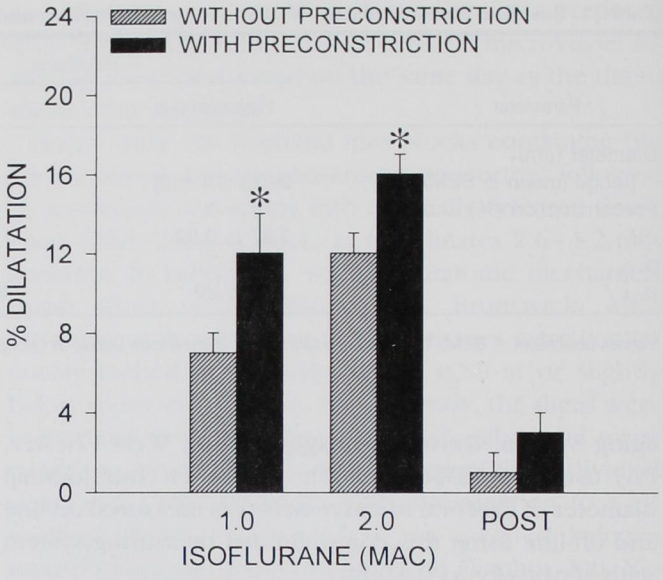

Fig. 1. Percent vasodilation from baseline (before preconstriction) of hippocampal microvessels in response to graded MAC levels of isoflurane in the presence and absence of vessel preconstriction with $PGF_{2\alpha}$. *$P < 0.05$ *versus* without preconstriction group. All dilation was statistically significant in both groups ($P < 0.05$) compared with baseline.

Resolution and visualization of cerebral microvessels were excellent in all slices that completed the protocol. Diameter measurements were reproducible and consistent between several independent, blinded observers in preliminary experiments. Experimental duration was typically less than 5 h. It has been previously demonstrated that the duration of slice viability in this preparation is greater than 10 h, with excellent preservation of vascular responsiveness as determined by the vasoconstrictive response to KCl administration.[22]

Halothane and isoflurane dilated, in a concentration-dependent fashion, hippocampal and neocortical microvessels. In the hippocampus (fig. 2A), the volatile agents produced a similar degree of vasodilation at 1 MAC (69 ± 6% and 79 ± 9%) and 2 MAC (120

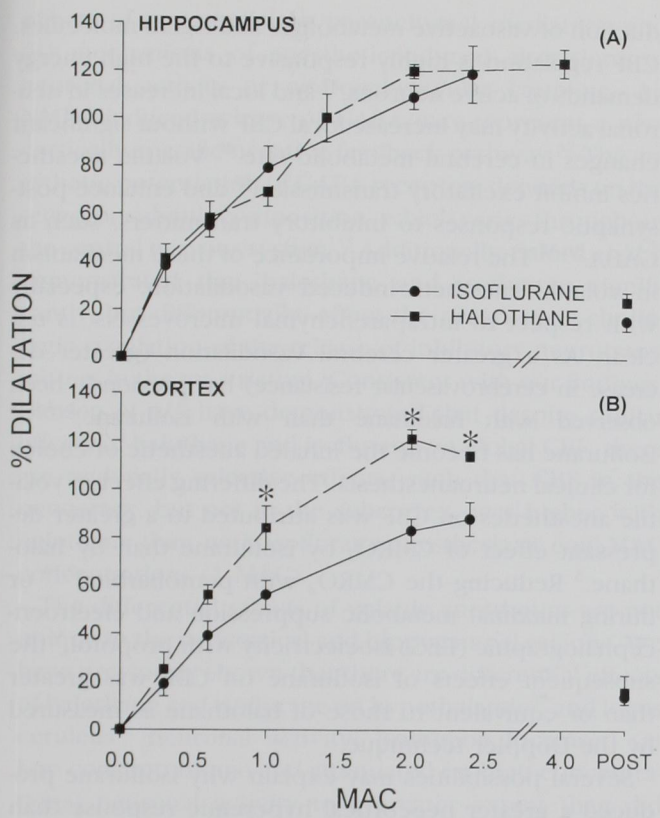

Fig. 2. Percent vasodilation of hippocampal microvessels (*A*) and neocortical microvessels (*B*) during various MAC levels (as determined by measured perfusate concentrations) of halothane and isoflurane. The data are normalized to the preconstriction produced by $PGF_{2\alpha}$. *$P < 0.05$ *versus* halothane treatment. Note the similar dilation of hippocampal vessels by agents and the greater dilation of neocortical vessels by halothane.

± 3% and 110 ± 5%) of halothane and isoflurane, respectively. There were no significant differences in the degree of dilation achieved between the two agents at any concentration. After discontinuation of the volatile agent administration, measured bath concentrations of halothane were 0.08 ± 0.02 mM and of isoflurane, 0.07 ± 0.01 mM, which corresponded to 0.2 MAC of each agent. Hippocampal microvessels were dilated to 24 ± 4% (halothane) and 16 ± 4% (isoflurane) at this time (*P* was not significant between groups).

However, in the neocortex (fig. 2B), halothane, at concentrations above 0.6 MAC, caused significantly greater vasodilation than did equi-MAC levels of isoflurane (84 ± 9% *vs.* 56 ± 6% dilation at 1 MAC; 121 ± 4% *vs.* 83 ± 5% dilation at 2 MAC halothane *vs.* isoflurane, respectively). After discontinuation of the anesthetics, measured bath concentrations of halothane corresponded to 0.2 MAC, and isoflurane corresponded to 0.1 MAC; cortical microvessels were dilated to 16 ± 7% (halothane) and 14 ± 3% (isoflurane) (*P* was not significant between groups).

Examining the previous data in an alternate fashion (by anesthetic agent rather than by region), halothane-induced microvessel dilation was similar in hippocampal and neocortical microvessels (58 ± 7% and 120 ± 3% in the hippocampus and 56 ± 4% and 121 ± 4% in the neocortex, at 0.6 and 2.0 MAC halothane, respectively) (fig. 3A). Isoflurane-mediated dilation was significantly more profound in hippocampal microvessels compared with effects in neocortical microvessels (38 ± 7% and 109 ± 5% in the hippocampus and 19 ± 5% and 83 ± 5% in the neocortex, at 0.3 and 2.0 MAC isoflurane, respectively; fig. 3B).

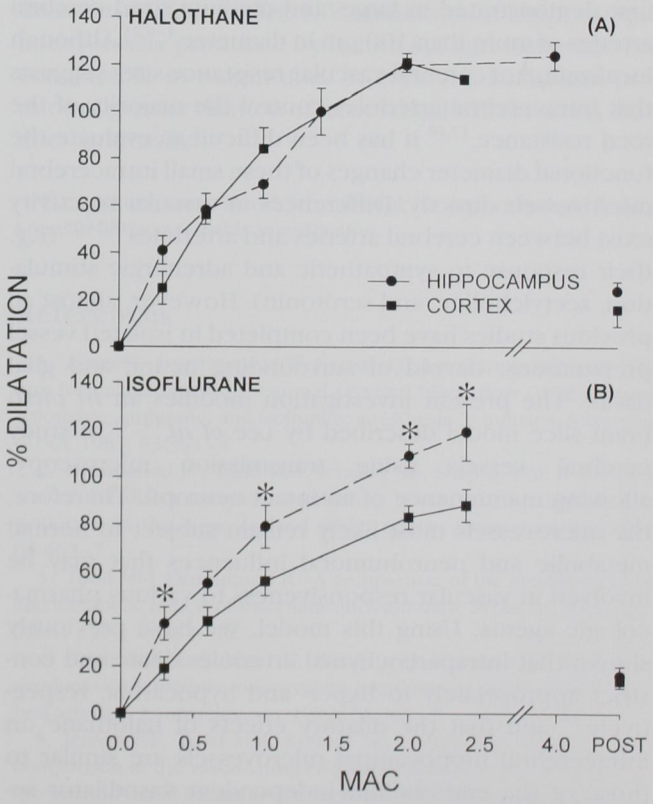

Fig. 3. Percent vasodilation of hippocampal and neocortical microvessels during various MAC levels (as determined by measured perfusate concentrations) of halothane (*A*) and isoflurane (*B*). The data are normalized to the preconstriction produced by $PGF_{2\alpha}$. *$P < 0.05$ *versus* cortical vascular response. Note the region-independent dilation by halothane and the greater dilation of hippocampal vessels compared with neocortical vessels by isoflurane.

Discussion

Halothane and isoflurane are effective cerebral arterial dilators in humans[1,9,12] and animals.[2-5] The present investigation compares, for the first time, the local vasodilation of intracerebral microvessels by these two anesthetics. The anesthetic-induced dilation, in addition to being potent and concentration-dependent, was agent- and region-specific. Although the effects of these agents were similar in hippocampal vessels, isoflurane was a less potent vasodilator than halothane in the cerebral cortex and was less potent at dilating cortical compared with hippocampal microvessels. These findings suggest that effects on intracerebral arterioles contribute to alterations in cerebrovascular resistance and flow produced by volatile anesthetics and are consistent with their previously ascribed regional heterogeneity in cerebral hyperemia.

The ability of halothane to dilate cerebral vessels was first demonstrated in large- and medium-sized cerebral arteries of more than 100 μm in diameter.[4-6,23] Although localization of cerebral vascular resistance sites suggests that intracerebral arterioles control the majority of the total resistance,[17,18] it has been difficult to evaluate the functional diameter changes of these small intracerebral microvessels directly. Differences in vascular reactivity exist between cerebral arteries and arterioles[18,24,25] (*e.g.* their response to sympathetic and adrenergic stimulation, acetylcholine, and serotonin). However, almost all previous studies have been completed in isolated vessel preparations, devoid of surrounding neural and glial tissue. The present investigation modifies an *in vitro* brain slice model described by Lee *et al.*[14-16] to study cerebral vessels using transmission microscopy, allowing maintenance of an intact neuropil. Therefore, the microvessels most likely remain subject to normal metabolic and neurohumoral influences that may be involved in vascular responsiveness to various pharmacologic agents. Using this model, we have previously shown that intraparenchymal arterioles dilate and constrict appropriately to hyper- and hypocarbia, respectively,[26] and that the dilatory effects of halothane on intracerebral hippocampal microvessels are similar to those of the endothelium-independent vasodilator sodium nitroprusside.[19]

The overall effect of volatile agents on the cerebral vasculature represents a balance between the direct, relaxing effects on vascular smooth muscle and a depression of spontaneous neuronal activity–cerebral metabolic rate, and the consequent changes in the production of vasoactive metabolites and signal molecules. CBF regulation is highly responsive to the high energy demands of active neurons,[27] and local increases in neuronal activity may increase local CBF without significant changes in cerebral metabolic rate.[28] Volatile anesthetics inhibit excitatory transmission[29] and enhance postsynaptic responses to inhibitory transmitters, such as GABA.[30,31] The relative importance of these mechanism in volatile anesthetic-induced vasodilation, especially with respect to intraparenchymal microvessels, is unclear. As a greater cerebral vasodilation (greater decrease in cerebrovascular resistance) has previously been observed with halothane than with isoflurane,[1-3,5,7,8] isoflurane has become the inhaled anesthetic of choice for clinical neuroanesthesia. The differing effect of volatile anesthetics on CBF was attributed to a greater depressant effect of $CMRO_2$ by isoflurane than by halothane.[3] Reducing the $CMRO_2$ with pentobarbital[2,10] or during maximal metabolic suppression and electroencephalographic (EEG) isoelectricity with propofol,[9] the subsequent effects of isoflurane on CBF was greater than or equivalent to those of halothane as measured by the Doppler technique.

Several possibilities may explain why isoflurane produced a greater neocortical hyperemic response than did halothane. First, the direct vasodilatory effects of the anesthetics may have been unmasked by the metabolic and functional depressant effect of the baseline barbiturate anesthesia.[10] Second, CBF was evaluated by laser Doppler flowmetry, which measures nondirectional perfusion by erythrocytes rather than by whole blood, and reflects flow in capillaries, arterioles, and venules of a small volume of superficial cortical tissue. The reasons for the discrepant results are unclear but may be related to the measurement of erythrocyte flow *versus* brain blood flow, the study of microvessels *versus* larger cerebral arteries, or as discussed previously, the potentially confounding effects of administration of a baseline barbiturate anesthetic. Our brain slice preparation specifically investigates the intraparenchymal arterioles that appear to respond in a manner similar to that of regional blood flow as described in previous *in vivo* studies in the absence of baseline anesthetics and metabolic suppression.[3,7,8] Because the vessels that we are studying are nonpressurized and nonperfused, this may have an impact on findings in this preparation.

The cause for regional differences in anesthetic-mediated vasodilation as observed in the present study is unclear, but may be related to (1) the sensitivity of the cellular mechanism(s) of vasorelaxation; (2) differential

effects of endothelial or parenchymal mediators; and (3) mechanisms of anesthetic-induced alterations of neuronal activity or neuronal-vascular coupling. An NMDA-induced release of GABA may represent a neocortically specific negative feedback pathway.[32] The anesthetic potentiation of GABA receptors depends on the receptor subunit composition, which varies throughout the central nervous system.[33] Additionally, Salord *et al.*[34] demonstrated that halothane and isoflurane significantly, but differentially, affect the presynaptic cholinergic regulation of the release of inhibitory neurotransmitters in the rat striatum. Consistent with our findings, Hansen *et al.*[8] have demonstrated that despite similar effects of halothane and isoflurane on global CBF, there are regionally selective effects, such that CBF in the neocortex, but not in the subcortex, was higher with halothane than with isoflurane anesthesia at equi-MAC concentrations (1 MAC).

The differential effects of volatile anesthetics are not unique to the neocortical and hippocampal regions. We have previously shown that there are differential effects of halothane and isoflurane on hypothalamic[35] and locus ceruleus[36] neuronal activity. Isoflurane increased (at low concentrations) and attenuated (at high concentrations) neuronal activity to a greater extent than did equivalent concentrations of halothane.[36]

Although the mechanisms of anesthetic-induced dilation of intracerebral microvessels have not been examined, Koenig *et al.*[37] used a closed cranial window with microscopy to assess the effects of volatile anesthetics on pial microvessels. Halothane[37] and isoflurane[38] produced nitric oxide-dependent dilation of pial arterioles. Additionally, nitric oxide may have a permissive role in halothane-induced cerebral hyperemia.[13] In large cerebral arteries, volatile anesthetic-induced vasodilation may be mediated, in part, by increases in cGMP levels[6] and vasodilatory prostanoids.[39] Whether there are regional variances in modulators of anesthetic-induced dilation or differences in the mechanism(s) by which volatile agents dilate these intraparenchymal microvessels is unknown and will be the subject of future investigations.

During the present experiments, the endogenous vasoconstrictor, $PGF_{2\alpha}$ was used to provide a physiologic baseline; myogenic tone and the vasodilatory responses were normalized to the amount of preconstriction. This method of calculation relies on the presence of very similar baseline vessel diameters and amount of preconstriction because the small diameters and diameter changes involved may otherwise result in significant errors. When using $PGF_{2\alpha}$ for preconstriction, physiologic vasodilatory effects to such factors as hypercarbia remain preserved.[26] Additionally, in previous isolated vessel experiments and in this brain slice preparation, vasodilatory responses to known vasoactive agents are best observed in the presence of preconstriction. The present results suggest that isoflurane produces dose-dependent increases in cerebral microvessel diameter in the presence and in the absence of preconstriction with $PGF_{2\alpha}$. The responses were qualitatively similar, but the degree of dilation was greater after preconstriction. Isoflurane also significantly vasodilates intraparenchymal microvessels after a different preconstriction method, with the pharmacologic vasoconstrictor, KCl.[22]

In conclusion, the present study demonstrates that halothane and isoflurane are potent and concentration-dependent dilators of intraparenchymal microvessels. There is regional and agent-specific heterogeneity in these vasodilatory effects. Vasodilation of hippocampal microvessels produced by halothane and isoflurane are comparable in magnitude. In contrast, halothane produces a greater dilation of neocortical microvessels than does isoflurane.

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