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Local Cerebral Blood Flow, Local Cerebral Glucose Utilization, and Flow–Metabolism Coupling during Sevoflurane versus *Isoflurane Anesthesia in Rats*

Christian Lenz, M.D., Annette Rebel, M.D.,* Klaus van Ackern, M.D.,† Wolfgang Kuschinsky, M.D.,‡ Klaus F. Waschke, M.D.§*

Background: **Compared to isoflurane, knowledge of local cerebral glucose utilization (LCGU) and local cerebral blood flow (LCBF) during sevoflurane anesthesia is limited.**

Methods: **LCGU, LCBF, and their overall means were measured in Sprague-Dawley rats (8 groups, n = 6 each) during sevoflurane and isoflurane anesthesia, 1 and 2 MAC, and in conscious control animals (2 groups, n = 6 each) using the autoradiographic 2-[^{14}C]deoxy-D-glucose and 4-iodo-N-methyl-[^{14}C]antipyrine methods.**

Results: **During anesthesia, mean cerebral glucose utilization was decreased: control, 56 ± 5 μmol · 100 g^{-1} · min^{-1}; 1 MAC isoflurane, 32 ± 4 μmol · 100 g^{-1} · min^{-1} (−43%); 1 MAC sevoflurane, 37 ± 5 μmol · 100 g^{-1} · min^{-1} (−34%); 2 MAC isoflurane, 23 ± 3 μmol · 100 g^{-1} · min^{-1} (−58%); 2 MAC sevoflurane, 23 ± 5 μmol · 100 g^{-1} · min^{-1} (−59%). Local analysis showed a reduction in LCGU in the majority of the 40 brain regions analyzed. Mean cerebral blood flow was increased as follows: control, 93 ± 8 ml · 100 g^{-1} · min^{-1}; 1 MAC isoflurane, 119 ± 19 ml · 100 g^{-1} · min^{-1} (+28%); 1 MAC sevoflurane, 104 ± 15 ml · 100 g^{-1} · min^{-1} (+12%); 2 MAC isoflurane, 149 ± 17 ml · 100 g^{-1} · min^{-1} (+60%); 2 MAC sevoflurane, 118 ± 21 ml · 100 g^{-1} · min^{-1} (+27%). LCBF was increased in most brain structures investigated. Correlation coefficients obtained for the relationship between LCGU and LCBF were as follows: control, 0.93; 1 MAC isoflurane, 0.89; 2 MAC isoflurane, 0.71; 1 MAC sevoflurane, 0.83; 2 MAC sevoflurane, 0.59).**

Conclusion: **Mean and local cerebral blood flows were lower during sevoflurane than during isoflurane anesthesia. This difference cannot be explained by differing changes in glucose utilization because glucose utilization was decreased to the same extent in both groups. (Key words: Animals; autoradiography; brain; volatile anesthetics.)**

THE low blood–gas solubility coefficient of sevoflurane promotes a fast recovery from anesthesia, and its nonirritant odor may reduce the possibility of coughing or straining during induction of anesthesia.[1,2] Therefore, sevoflurane may be an attractive volatile agent for use during neurosurgery. However, compared with the established volatile agent in neuroanesthesia, isoflurane, far less is known about the cerebral effects of sevoflurane. Many previous studies on cerebral blood flow (CBF) and cerebral metabolism during sevoflurane anesthesia have either reported global values, which were obtained by the Kety-Schmidt technique in humans,[3] or mainly cortical values, which were obtained by the sagittal sinus sampling technique[4–6] in animals. Additional studies in rats using microspheres[7,8] have also been confined to global values for CBF. The results of these studies showed a decrease of cerebral metabolism between 20–52%[3,4] and mostly no changes[5–7] or a decrease of CBF by 20–34%[3,4] during sevoflurane anesthesia under the different study conditions investigated. Regional CBF during sevoflurane anesthesia has been measured by Manohar using microspheres in swine[4] and by Yoshikawa *et al.*[9] using positron emission tomography (PET) in rhesus monkeys, although both studies lack a comparison with another volatile anesthetic,[4,9] and in the PET study of Yoshikawa *et al.* a conscious control group is lacking.[9] In the present investigation the effects of sevoflurane and isoflurane anesthesia on local cerebral glucose utilization (LCGU) and local cerebral blood flow (LCBF)

* Research Fellow, Department of Anesthesiology, Faculty of Clinical Medicine, Mannheim.

† Professor of Anesthesiology and Chair, Department of Anesthesiology, Faculty of Clinical Medicine, Mannheim.

‡ Professor of Physiology and Chair, Department of Physiology, Faculty of Medicine, Heidelberg.

§ Research Coordinator Department of Anesthesiology, Faculty of Clinical Medicine, Mannheim.

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Address reprint requests to Dr. Lenz: Department of Physiology, University of Heidelberg, Im Neuenheimer Feld 326, D-69120 Heidelberg, Germany. Address electronic mail to: jr1@ix.urz.uni-heidelberg.de

have been compared with conscious control animals using the quantitative autoradiographic 2-[^{14}C]deoxy-D-glucose and 4-iodo-N-methyl-[^{14}C]antipyrine methods in rats. These methods yield a high spatial resolution and allow the examination of the coupling between CBF and glucose metabolism for a range of LCGU and LCBF.

Materials and Methods

After approval by the institutional animal care committee (Regierungspräsidium Karlsruhe, Germany), the experiments were performed on 60 male Sprague-Dawley rats (Charles River Deutschland, Sulzfeld, Germany), weighing 319 ± 41 g (mean ± SD). The animals were kept under temperature-controlled environmental conditions on a 14:10 light–dark cycle and fed a standard diet (Altromin 1324, Altromin, Lage, Germany) with free access to food and potable water until the start of the experiments.

The rats were randomly assigned to one of five experimental groups: conscious control, isoflurane 1.0 or 2.0 MAC, or sevoflurane 1.0 or 2.0 MAC. They were placed in a small box and anesthetized by inhalation of isoflurane (Forene, Abbott, Wiesbaden, Germany) or sevoflurane (Sevorane, Abbott) and 30% O_2/air with precalibrated vapors (isoflurane, Fortec, Cyprane Keighley, UK; sevoflurane, Dräger, Lübeck, Germany). Anesthesia for surgery was maintained by 1.5–2.5% isoflurane or 2.5–4% sevoflurane *via* a nose cone. Body temperature was held at 37°C with a temperature-controlled heating pad. Polyethylene catheters (PE-50; Labokion, Sinsheim, Germany) were inserted into the right femoral artery and vein. A tracheostomy tube was inserted and connected to a small rodent ventilator (KTR-4; Hugo Sachs Elektronik, Freiburg, Germany). All wound sites were covered with a 2% lidocaine ointment. The arterial catheter was connected to a pressure transducer for continuous blood pressure monitoring, whereas the venous catheter was used for drug and fluid administration. Rats in the control groups were anesthetized with halothane (Fluothane, Zeneca, Plankstadt, Germany), N_2O 70%, and O_2. Anesthesia for surgery was maintained by 1.0–1.5% halothane. Until the end of surgery, these animals were treated like the animals in the isoflurane and sevoflurane groups, but insertion of a tracheostomy tube was omitted. After surgery, these control animals were placed in rat restrainers (Braintree Scientific, Braintree, MA), infused with saline (4 ml · kg^{-1} body weight (bw) · h^{-1}), and allowed to recover for a minimum of 3 h before measurement of cerebral glucose utilization (CGU) and CBF.

After surgery in the isoflurane and sevoflurane groups, the concentration of the anesthetic agent was set to the intended MAC level. For isoflurane, a MAC value of 1.4%[10] was used in this study. MAC values for sevoflurane in different strains of rats have been reported to range from 2.2% to 2.8%.[8,11–13] In Sprague-Dawley rats, Crawford *et al.* determined a MAC value of 2.4% for sevoflurane use.[8] Because Sprague-Dawley rats were also used in the present study, a MAC value of 2.4% for sevoflurane was used.

To achieve a steady state, anesthesia was maintained for equilibration periods of an additional 45 min in the LCGU studies and 60 min in the LCBF studies before the start of the infusion of either [^{14}C]deoxyglucose or [^{14}C]iodoantipyrine. This difference in the administration time of the isotopic tracers was chosen to achieve approximately even median points of the tracer measurement.[14] One half of the [^{14}C]deoxyglucose uptake and phosphorylation occurs during the first 10–15 min of the 45-min measurement period,[15] whereas the infusion of [^{14}C]iodoantipyrine takes only 1 min. Preliminary experiments had shown that some rats exhibited a tendency for spontaneous breathing during mechanical ventilation at 1 MAC sevoflurane anesthesia, although no other sign for light anesthesia, *e.g.*, body movements, could be observed in these animals throughout the experiments. Therefore 20 min before the start of the [^{14}C]deoxyglucose or [^{14}C]iodoantipyrine infusions, pancuronium bromide (Pancuronium, Organon, Eppelheim, Germany) was administered for muscle relaxation. Simultaneously 4 ml · kg^{-1} bw · h^{-1} of saline was infused between the start of surgery and the start of isotopic tracer infusions. Blood gas levels were measured using an automated blood gas analyzer (AVL Gas Check 939, AVL, Graz, Austria). Expiratory CO_2 was continuously monitored by a capnometer (EMG I, Heyer, Bad Ems, Germany). The hematocrit was determined by capillary tube centrifugation (Hettich, Tuttlingen, Germany). Plasma glucose concentration was measured by a polarographic method (Glucose Analyzer 2, Beckmann, München, Germany). The ventilator was adjusted to maintain normoxia and normocapnia. Body temperature was monitored *via* a rectal probe and maintained within the range of 36.5–37.5°C with a heating lamp.

For the measurement of LCGU, 125 μCi/kg bw of 2-[^{14}C]deoxy-D-glucose (specific activity 50–60 mCi/mmol; American Radiolabeled Chemicals, St. Louis, MO) dissolved in 1 ml of saline was injected as a pulse *via* the femoral venous catheter within 20 s, and timed arterial blood samples of approximately 80 μl each were collected through the femoral arterial catheter at 15, 30,

and 45 s and at 1, 2, 3, 5, 7.5, 10, 25, 35, and 45 min. The blood samples were centrifuged immediately and stored on ice until assays for plasma 2-[^{14}C]deoxy-D-glucose and glucose concentrations were performed as previously described.[15] Immediately after the final arterial blood sample was collected, the animal was decapitated, and the brain was rapidly removed and frozen in 2-methylbutane chilled from −40 to −50°C.

For the measurement of LCBF, 100 μCi/kg bw of 4-iodo-N-methyl-[^{14}C]antipyrine (specific activity 55 mCi/mmol; American Radiolabeled Chemicals) dissolved in 1 ml of saline was infused continuously at a progressively increasing infusion rate for 1 min *via* the femoral venous catheter. The progressively increasing infusion rate, a modification of the method described earlier,[16] was chosen to minimize equilibration of rapidly perfused tissues with arterial blood during the period of measurement. During the 1-min infusion period, 14–20 timed blood samples were collected in drops from the free-flowing arterial catheter directly onto filter paper disks (diameter, 1.3 cm) that previously had been placed in small plastic beakers and weighed. The samples were weighed and radioactivity estimated with a liquid scintillation counter (Tri-Carb 4000 series, Canberra Packard, Frankfurt, Germany) after extraction of the radioactive compound with ethanol. After the 1-min infusion and sampling period, the animal was decapitated, and the brain was removed as quickly as possible and frozen in the same manner as described for the 2-[^{14}C]-deoxy-D-glucose experiments.

In both the 2-[^{14}C]-deoxy-D-glucose and 4-iodo-N-methyl-[^{14}C]antipyrine experiments, the frozen brains were coated with chilled embedding medium (M1 embedding matrix, Lipshaw, Detroit, MI), stored at −80°C in plastic bags, sectioned into 20-μm sections at −20°C in a cryostat, and autoradiographed along with precalibrated [^{14}C]methyl methacrylate standards. Autoradiographic images were converted to digitized optical density images by an image processing system (MCID, Imaging Research, St. Catharines, Canada). Tissue optical densities were converted to [^{14}C] concentration by comparison with the precalibrated standards. LCGU or LCBF were calculated from the local concentrations of [^{14}C] and the time course of plasma 2-[^{14}C]-deoxy-D-glucose and glucose concentrations,[15] with a lumped constant of 0.483, or the time course of the blood 4-iodo-N-methyl-[^{14}C]antipyrine, including corrections for the lag and washout in the arterial catheter.[16] The washout correction rate constant was 100/min. A brain–blood partition coefficient for iodo[^{14}C]antipyrine of 0.9 was used as previously determined in our strain of rats.[17]

For measurements of separate brain structures, an ellipsoid cursor was used and adjusted to the size of the individual region. For measurement of mean CGU or mean CBF, coronal sections were analyzed as a whole at distances of 200 μm, and the values were summarized to obtain the area-weighted means of all measured sections.

Statistical Analysis

Statistical differences between the experimental groups were evaluated by analysis of variance according to the procedures described by Wallenstein *et al.*[18] Mean CGU and mean CBF obtained at different MAC levels were compared for each anesthetic separately (comparison of three groups each with Bonferroni correction for multiple comparisons). In addition, mean CGU and mean CBF of the two anesthetics were compared at each MAC level (comparison of two groups at the same MAC level). Significance was assumed for $P < 0.05$. Data are presented as mean ± SD. The overall relationship between LCGU and LCBF in the examined regions of the brain was assessed by the least-squares fit of the data to $y = ax + b$ where x is the mean LCGU in a given region and y is mean LCBF in that area. Because LCGU and LCBF values from multiple brain structures in a single animal are not independent from each other, it was not tried to apply statistical comparisons to data relying on such measurements in the local and the coupling analyses (slopes and intercepts).

Results

Physiologic Parameters

Physiologic parameters of the different groups are summarized in table 1. Mean arterial blood pressure was significantly decreased with increasing MAC of both anesthetics. Plasma glucose concentration was increased, and heart rate was decreased parallel to increasing anesthetic depth. All other physiologic parameters were not significantly changed.

Metabolic Studies

Mean Cerebral Glucose Utilization. Figure 1 shows the mean CGU in the different experimental groups (bottom). Compared with the conscious state, mean CGU was significantly reduced with both anesthetics at both MAC levels. At 1 MAC, mean CGU was decreased to 57% of control for isoflurane and to 66% for sevoflurane ($P < 0.05$), and at 2 MAC to 42% for isoflurane and to 41% for sevoflurane.

Table 1. Physiological Parameters During Isoflurane and Sevoflurane Anesthesia

Measurement	Control	1 MAC		2 MAC	
		Isoflurane	Sevoflurane	Isoflurane	Sevoflurane
LCGU group					
Pa_{O_2} (mmHg)	91 ± 4	113 ± 17	112 ± 19	113 ± 19	112 ± 19
Pa_{CO_2} (mmHg)	40 ± 3	40 ± 2	39 ± 2	40 ± 2	42 ± 1
*p*H	7.41 ± 0.01	7.43 ± 0.04	7.40 ± 0.03	7.41 ± 0.05	7.43 ± 0.03
Hematocrit (%)	42 ± 3	43 ± 3	40 ± 2	42 ± 2	40 ± 1
Plasma glucose concentration (mg/dl)	158 ± 17	191 ± 16*	188 ± 19	218 ± 27*	208 ± 21*
Heart rate (min^{-1})	378 ± 25	382 ± 36	340 ± 28	347 ± 24	341 ± 18
Mean arterial blood pressure (mmHg)	137 ± 13	103 ± 7*	96 ± 12*	84 ± 12*	80 ± 5*
LCBF group					
Pa_{O_2} (mmHg)	93 ± 5	101 ± 19	103 ± 24	99 ± 14	115 ± 28
Pa_{CO_2} (mmHg)	41 ± 2	40 ± 2	40 ± 2	39 ± 2	41 ± 2
*p*H	7.41 ± 0.02	7.40 ± 0.04	7.44 ± 0.04	7.38 ± 0.04	7.41 ± 0.04
Hematocrit (%)	42 ± 2	41 ± 3	41 ± 1	40 ± 2	40 ± 1
Plasma glucose concentration (mg/dl)	160 ± 24	178 ± 24	206 ± 29*	189 ± 15	196 ± 21
Heart rate (min^{-1})	431 ± 48	362 ± 56*	359 ± 24*	362 ± 39*	342 ± 30*
Mean arterial blood pressure (mmHg)	138 ± 10	88 ± 24*	98 ± 9*	79 ± 8*	73 ± 9*

Values are mean ± SD of n = 6 in each of 5 groups for LCGU measurements and each of 5 groups for LCBF measurements.

* $P < 0.05$ *versus* control group (ANOVA with Bonferroni correction for LCGU and LCBF groups separately).

Local Cerebral Glucose Utilization. The considerable decrease in CGU observed during isoflurane and sevoflurane anesthesia for the whole brain was also reflected on a local level in the majority of brain structures investigated (table 2). In contrast to the general depression of CGU obtained in most brain structures, an increase was measured in the medial habenula, hippocampus CA3 and CA4 regions, and substantia nigra compact part during administration of both isoflurane and sevoflurane anesthesia at 2 MAC. In addition during 2 MAC sevoflurane anesthesia, LCGU was also increased in the interpeduncular nucleus.

Blood Flow Studies

Mean Cerebral Blood Flow. Figure 1 shows the mean CBF in the different experimental groups (top). Compared with the conscious state, mean CBF was increased with both anesthetics at both MAC levels. The increase in mean CBF was more pronounced during isoflurane anesthesia than during sevoflurane anesthesia at 2 MAC ($P < 0.05$). At this concentration, mean CBF compared with control was increased by 60% during isoflurane anesthesia and by 27% during sevoflurane anesthesia.

Local Cerebral Blood Flow. The increase in CBF observed for the whole brain during isoflurane and sevoflurane anesthesia was also reflected on a local level in parts of the 40 brain structures investigated at 1 MAC and in most of them at 2 MAC (table 3). A lack of change or a decrease of LCBF was found at 2 MAC mainly in cortical structures. During sevoflurane anesthesia, LCBF was lower than during isoflurane anesthesia in parts of the brain structures at 1 MAC and in most of them at 2 MAC.

Coupling between Local Cerebral Blood Flow and Local Cerebral Glucose Utilization. At 1 MAC of isoflurane and sevoflurane administration, a close coupling between CBF and glucose metabolism could be demonstrated in all 40 brain structures analyzed (fig. 2). At 2 MAC, coupling was preserved in all brain regions, except for those that showed an increased metabolism during either isoflurane or sevoflurane anesthesia (medial habenula, hippocampus CA3 and CA4 regions, substantia nigra, compact part, and interpeduncular nucleus). This resulted in lower correlation coefficients for the relationship between LCBF and LCGU at 2 MAC than at 1 MAC.

Discussion

The present study shows that sevoflurane and isoflurane induce a decrease in glucose utilization and an increase in blood flow of the brain. However, these effects are less

Table 2. Local Cerebral Glucose Utilization ($\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$)

		1 MAC		2 MAC	
	Control (n = 6)	Isoflurane (n = 6)	Sevoflurane (n = 6)	Isoflurane (n = 6)	Sevoflurane (n = 6)
Cerebellum					
Cerebellar cortex	41 ± 5	25 ± 4	29 ± 3	22 ± 3	24 ± 5
Dentate nuclei	76 ± 8	53 ± 8	63 ± 6	76 ± 22	61 ± 14
Medulla-pons					
Vestibular nucleus	90 ± 12	71 ± 6	79 ± 13	69 ± 11	48 ± 8
Superior olive	86 ± 14	75 ± 14	73 ± 9	63 ± 12	40 ± 7
Pontine gray	45 ± 6	25 ± 4	30 ± 3	22 ± 1	24 ± 5
Lateral lemniscus	68 ± 10	44 ± 14	40 ± 16	33 ± 11	29 ± 4
Mesencephalon					
Inferior colliculus	111 ± 17	65 ± 7	62 ± 6	38 ± 5	32 ± 9
Superior colliculus	64 ± 9	34 ± 4	40 ± 3	29 ± 2	28 ± 8
Substantia nigra, compact part	58 ± 8	49 ± 5	58 ± 8	60 ± 17	60 ± 10
Substantia nigra, reticular part	41 ± 5	26 ± 5	33 ± 3	25 ± 7	28 ± 8
Interpeduncular nucleus	83 ± 10	62 ± 32	100 ± 19	74 ± 40	119 ± 11
Diencephalon					
Medial geniculate	90 ± 12	34 ± 7	35 ± 4	21 ± 4	22 ± 6
Lateral geniculate	71 ± 10	29 ± 6	31 ± 2	21 ± 4	22 ± 5
Mamillary body	74 ± 7	53 ± 9	52 ± 8	47 ± 8	41 ± 5
Hypothalamus	39 ± 5	24 ± 4	30 ± 3	21 ± 3	24 ± 5
Ventral thalamus	77 ± 6	39 ± 5	40 ± 6	27 ± 3	28 ± 7
Lateral thalamus	74 ± 7	34 ± 6	36 ± 4	25 ± 4	31 ± 4
Medial habenula	64 ± 6	59 ± 6	62 ± 8	97 ± 18	84 ± 10
Lateral habenula	89 ± 16	49 ± 4	52 ± 7	49 ± 4	48 ± 4
Telencephalon					
Hippocampus CA1	54 ± 8	37 ± 10	48 ± 7	26 ± 5	28 ± 6
Hippocampus CA2	45 ± 10	29 ± 6	37 ± 3	22 ± 5	25 ± 6
Hippocampus CA3	50 ± 8	47 ± 11	56 ± 12	55 ± 11	68 ± 12
Hippocampus CA4	57 ± 5	50 ± 10	63 ± 14	73 ± 13	84 ± 16
Dentate gyrus	41 ± 4	31 ± 7	37 ± 5	23 ± 3	25 ± 5
Amygdaloid complex	40 ± 5	22 ± 5	27 ± 3	17 ± 3	18 ± 6
Globus pallidus	41 ± 5	26 ± 6	31 ± 3	21 ± 5	22 ± 6
Caudate nucleus	80 ± 10	46 ± 7	44 ± 5	26 ± 3	24 ± 5
Nucleus accumbens	71 ± 12	45 ± 7	48 ± 7	24 ± 3	25 ± 5
Lateral septal nuclei	40 ± 7	25 ± 2	30 ± 3	22 ± 3	22 ± 4
Cingulate cortex	86 ± 14	37 ± 7	43 ± 6	20 ± 3	21 ± 5
Visual cortex	79 ± 5	43 ± 5	47 ± 6	22 ± 4	22 ± 6
Auditory cortex	113 ± 10	47 ± 8	57 ± 8	24 ± 4	23 ± 6
Parietal cortex	76 ± 8	42 ± 6	47 ± 4	22 ± 4	22 ± 5
Sensory motor cortex	81 ± 10	35 ± 4	42 ± 3	22 ± 4	23 ± 6
Frontal cortex	80 ± 9	34 ± 4	42 ± 4	22 ± 4	22 ± 6
Pyriform cortex	76 ± 4	33 ± 7	40 ± 8	21 ± 5	21 ± 5
Myelinated fiber tracts					
Internal capsule	21 ± 3	9 ± 4	14 ± 1	8 ± 2	7 ± 4
Corpus callosum	27 ± 4	14 ± 4	21 ± 3	11 ± 3	10 ± 5
Genu of corpus callosum	22 ± 5	13 ± 7	16 ± 2	11 ± 3	8 ± 4
Cerebellar white matter	24 ± 8	14 ± 5	17 ± 2	12 ± 3	13 ± 5

Values are means ± SD.

pronounced for sevoflurane than for isoflurane. During sevoflurane anesthesia, the reduction in glucose utilization at 1 MAC and the increase in blood flow at 2 MAC were less than during isoflurane anesthesia. The smaller increase in CBF during 2 MAC sevoflurane anesthesia than during 2 MAC isoflurane anesthesia cannot be explained by differences in cerebral metabolism because glucose utilization was identical in both groups. Local analysis of the coupling between LCGU and LCBF showed a preservation of the tight coupling in all brain structures analyzed at 1 MAC and in most brain structures also at 2 MAC during sevoflurane and isoflurane anesthesia.

Table 3. Local Cerebral Blood Flow (ml · 100 g^{-1} · min^{-1})

	Control (n = 6)	1 MAC		2 MAC	
		Isoflurane (n = 6)	Sevoflurane (n = 6)	Isoflurane (n = 6)	Sevoflurane (n = 6)
Cerebellum					
Cerebellar cortex	82 ± 10	126 ± 28	115 ± 25	216 ± 30	161 ± 29
Dentate nuclei	151 ± 10	215 ± 55	230 ± 47	340 ± 72	310 ± 42
Medulla-pons					
Vestibular nucleus	146 ± 23	225 ± 46	282 ± 90	304 ± 62	303 ± 107
Superior olive	157 ± 27	251 ± 53	228 ± 46	373 ± 109	309 ± 86
Pontine gray	95 ± 9	122 ± 30	96 ± 13	185 ± 48	159 ± 41
Lateral lemniscus	156 ± 26	163 ± 60	96 ± 14	224 ± 97	190 ± 77
Mesencephalon					
Inferior colliculus	177 ± 15	229 ± 47	181 ± 28	340 ± 121	229 ± 52
Superior colliculus	110 ± 8	132 ± 24	116 ± 18	203 ± 40	156 ± 31
Substantia nigra, compact part	96 ± 16	120 ± 20	109 ± 18	206 ± 56	146 ± 24
Substantia nigra, reticular part	75 ± 12	93 ± 13	87 ± 13	143 ± 38	110 ± 20
Interpenduncular nucleus	141 ± 35	180 ± 36	212 ± 44	288 ± 67	250 ± 41
Diencephalon					
Medial geniculate	148 ± 17	149 ± 26	121 ± 20	221 ± 53	148 ± 23
Lateral geniculate	115 ± 9	120 ± 22	104 ± 14	173 ± 26	129 ± 19
Mamillary body	119 ± 13	153 ± 17	167 ± 33	203 ± 33	183 ± 29
Hypothalamus	83 ± 8	94 ± 10	92 ± 15	130 ± 22	107 ± 15
Ventral thalamus	110 ± 9	136 ± 25	106 ± 18	173 ± 13	128 ± 30
Lateral thalamus	129 ± 13	129 ± 31	107 ± 16	174 ± 20	129 ± 20
Medial habenula	129 ± 18	159 ± 32	166 ± 33	224 ± 17	185 ± 40
Lateral habenula	160 ± 18	173 ± 32	166 ± 46	253 ± 12	198 ± 45
Telencephalon					
Hippocampus CA1	72 ± 10	119 ± 34	115 ± 37	157 ± 25	112 ± 20
Hippocampus CA2	73 ± 13	112 ± 33	109 ± 35	148 ± 26	112 ± 16
Hippocampus CA3	84 ± 9	121 ± 21	118 ± 25	178 ± 38	141 ± 18
Hippocampus CA4	75 ± 10	110 ± 21	107 ± 23	163 ± 28	128 ± 23
Dentate gyrus	70 ± 8	103 ± 23	101 ± 18	134 ± 26	104 ± 18
Amygdaloid complex	79 ± 9	90 ± 9	92 ± 18	113 ± 12	84 ± 11
Globus pallidus	59 ± 3	84 ± 18	82 ± 16	118 ± 20	85 ± 14
Caudate nucleus	103 ± 8	121 ± 21	99 ± 14	141 ± 11	115 ± 23
Nucleus accumbens	105 ± 7	125 ± 22	114 ± 26	143 ± 11	103 ± 18
Lateral septal nuclei	82 ± 8	102 ± 16	90 ± 17	139 ± 11	119 ± 21
Cingulate cortex	142 ± 17	133 ± 19	114 ± 17	143 ± 10	108 ± 23
Visual cortex	114 ± 13	128 ± 28	98 ± 12	128 ± 26	98 ± 20
Auditory cortex	177 ± 12	135 ± 22	104 ± 16	129 ± 24	103 ± 26
Parietal cortex	125 ± 9	125 ± 24	101 ± 16	125 ± 27	98 ± 24
Sensory motor cortex	134 ± 8	132 ± 26	107 ± 17	153 ± 14	113 ± 15
Frontal cortex	127 ± 11	132 ± 22	112 ± 18	155 ± 17	104 ± 17
Pyriform cortex	104 ± 8	109 ± 19	102 ± 24	125 ± 7	86 ± 13
Myelinated fiber tracts					
Internal capsule	40 ± 3	58 ± 12	51 ± 9	83 ± 8	65 ± 13
Corpus callosum	36 ± 5	55 ± 8	45 ± 6	78 ± 5	60 ± 9
Genu of corpus callosum	41 ± 4	64 ± 11	54 ± 10	86 ± 7	63 ± 9
Cerebellar white matter	41 ± 6	72 ± 20	64 ± 12	104 ± 12	89 ± 13

Values are mean ± SD.

Metabolic Studies

The decrease of mean CGU by 34% at 1 MAC and 59% at 2 MAC during sevoflurane anesthesia is in the range obtained in previous studies for global cerebral metabolic rate of oxygen ($CMRO_2$) in humans (52%),[3] pigs (50–52%),[4] rabbits (50%),[6] and dogs (30%).[5] However, a direct comparison is not possible because either additional anesthetics[3,6] or lightly anesthetized control animals were used.[5,6]

Comparison of the mean CGU measured during isoflurane anesthesia with that obtained during sevoflurane anesthesia shows a slightly (−9%), although signifi-

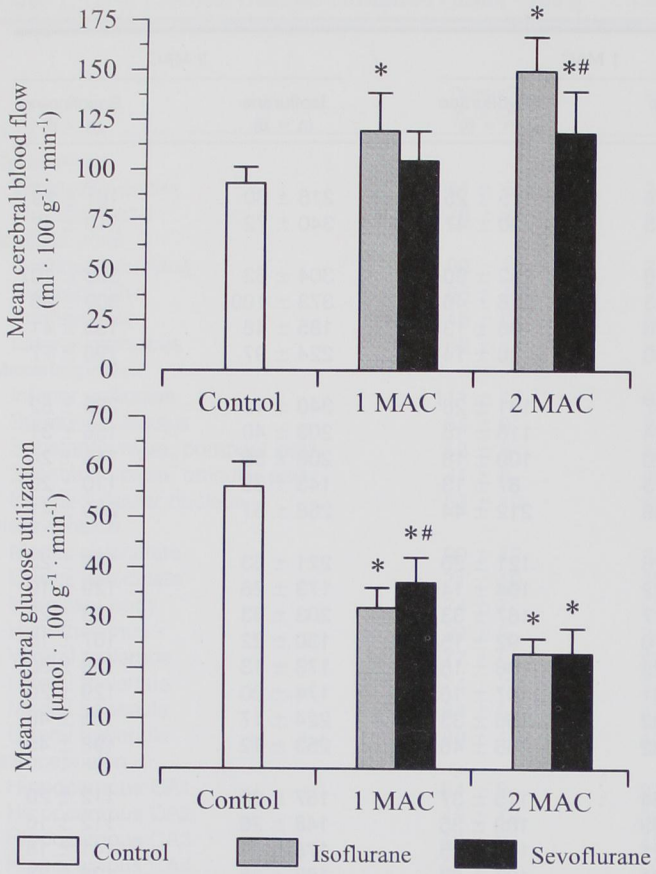

Fig. 1. Mean cerebral glucose utilization (*bottom*) and mean cerebral blood flow (*top*) during 1 and 2 MAC isoflurane and sevoflurane anesthesia (mean ± SD; n = 6 in each group). Significant ($P < 0.05$) difference *from conscious control (ANOVA with Bonferroni correction for isoflurane and sevoflurane separately), #sevoflurane *versus* isoflurane (ANOVA for each MAC value of isoflurane and sevoflurane separately).

cantly, lower CGU during 1 MAC sevoflurane than during 1 MAC isoflurane anesthesia. Small differences have also been found between the capacity of isoflurane and sevoflurane to reduce $CMRO_2$ between 1 and 1.5 MAC in rabbits[6] and dogs,[5] as measured by the sagittal sinus outflow technique. However, quantitative values of $CMRO_2$ have only been reported in rabbits (isoflurane, 3.01 ± 0.62 $mlO_2 \cdot 100\ g^{-1} \cdot min^{-1}$ *vs.* sevoflurane, 2.49 ± 0.62 $mlO_2 \cdot 100\ g^{-1} \cdot min^{-1}$),[6] although no statement was given concerning the significance of this difference.

Mean values of cerebral glucose metabolism as given in a number of previous studies are of limited value if local changes in metabolism occur in specific brain structures. Local changes of glucose metabolism have been detected in the present study during isoflurane and sevoflurane anesthesia. Concerning isoflurane anesthesia, values of LCGU were comparable with those of previous autoradiographic investigations in rats, which showed either nearly identical[19] or slightly higher values.[20] A decrease of glucose metabolism in the majority of brain structures combined with an unchanged or increased glucose metabolism in a few distinct brain structures is a rather common finding for a number of volatile and nonvolatile anesthetics when the [^{14}C]deoxyglucose method is used. An unchanged or increased LCGU has been found in the habenulointerpeduncular system (medial habenula, habenulointerpeduncular tract, interpeduncular nucleus) for alphaxalone,[21] pentobarbital,[22,23]

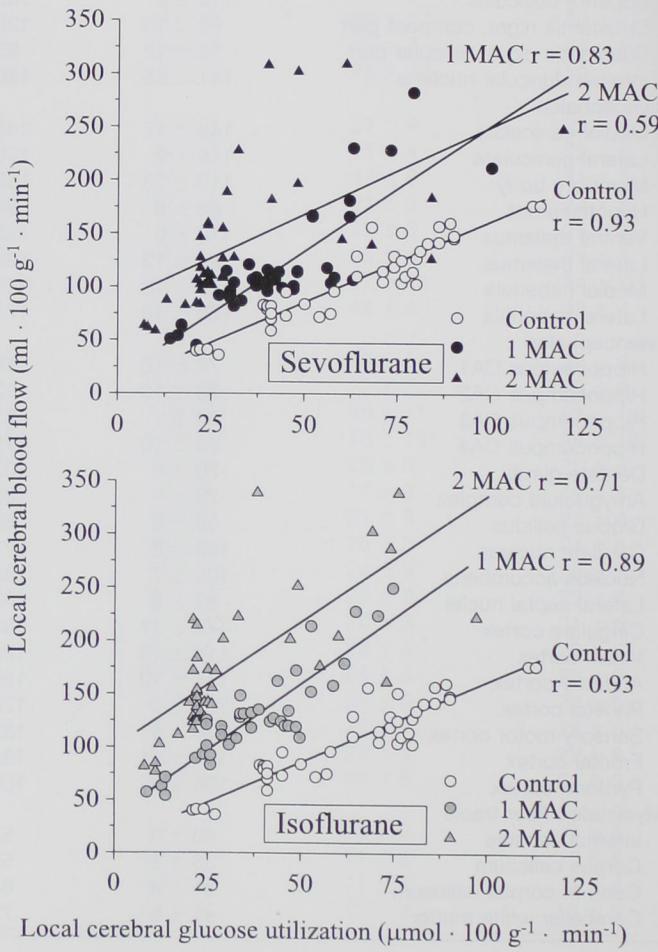

Fig. 2. Coupling of local cerebral blood flow (LCBF) to local cerebral glucose utilization (LCGU) in 40 brain structures during 1 and 2 MAC isoflurane anesthesia (*bottom*) and sevoflurane anesthesia (*top*) compared with conscious control rats (n = 6 for each LCGU value and each LCBF value at all MAC levels). The regression lines were calculated according to y = ax + b, where y is LCBF and x is LCGU. Control: y = 1.5 x +9.9, isoflurane 1 MAC: y = 2.5 x +34.4, isoflurane 2 MAC: y = 2.4 x +99.1, sevoflurane 1 MAC: y = 2.3 x +16.7, sevoflurane 2 MAC: y = 1.6 x +86.1.

ketamine,[24] chloral hydrate,[22] ether,[22] halothane,[25,26] enflurane,[27,28] isoflurane,[19,20] and for sevoflurane anesthesia in the present study. Further exceptions from a general decrease in glucose metabolism have been found in brain stem nuclei of the auditory system, the superficial layers of the superior colliculus, and oculomotor nuclei during pentobarbital anesthesia[22] and in the substantia nigra, compact part, and hippocampus CA3 and CA4 regions during volatile anesthetics.[19,20,25–30] In principle, such a finding could reflect a stage of excitement that has been observed during light anesthesia with halothane.[26] However, the concentrations of anesthetics selected in the present study were high enough to exclude a state of light anesthesia. Therefore it appears more likely to explain the relative increase of LCGU in some brain structures by a decreased inhibitory nervous outflow from some brain regions induced by the general depression of glucose metabolism. This decreased inhibitory influence could result in an increased glucose utilization in the corresponding regions of the brain.

Blood Flow Studies

Previous data on CBF during sevoflurane anesthesia are not consistent. At 1 and 1.5 MAC, a decrease of CBF has been found in pigs during sevoflurane anesthesia.[4] In spontaneously breathing rats exhibiting a Pa_{CO_2} of 48 mmHg, an increase in CBF has been reported.[8] Other studies have not found a significant increase of CBF during sevoflurane anesthesia at MAC values ranging from 0.5 to 1.7 in dogs,[5] rabbits,[6] and rats.[7] The results of the present study are consistent with the latter findings. Apart from the present study, CBF has been only investigated at a higher MAC value of sevoflurane in dogs. No increase of CBF during sevoflurane anesthesia could be measured at 2.14 MAC compared with 0.5 MAC sevoflurane.[5] However, no increase of CBF was also observed during isoflurane anesthesia at comparable conditions in this study, which contrasts with many other studies investigating CBF during isoflurane anesthesia.[7,19,31–35]

Coupling between Local Cerebral Blood Flow and Local Cerebral Glucose Utilization

The present investigation shows the preservation of a close coupling between LCBF and LCGU during conscious control conditions, which is in accordance with previous studies.[36] During anesthesia induced by 1 MAC isoflurane or sevoflurane, the local coupling between LCGU and LCBF is preserved, although the relationship is reset to higher levels of blood flow. These findings confirm those of Hansen *et al.*,[14] who have demonstrated a preserved local flow–metabolism coupling during 1 MAC halothane and isoflurane anesthesia. The present study shows that comparable results are obtained during 1 MAC of sevoflurane anesthesia. During 2 MAC of isoflurane and sevoflurane anesthesia, some brain structures in which higher rates of metabolism could be measured during anesthesia than in the conscious state (medial habenula, hippocampus CA3 and CA4 regions, substantia nigra, compact part during isoflurane and sevoflurane anesthesia and the interpeduncular nucleus during sevoflurane anesthesia) seemed to escape the pattern of flow–metabolism coupling observed at 1 MAC. Although blood flow values measured in these structures at 2 MAC were increased when compared with blood flow values obtained in the conscious state, these values did not reach the level predicted by the coupling pattern of the remaining majority of brain structures at 2 MAC. However, this did not indicate a compromised oxygen delivery to the brain because the ratio of LCBF to LCGU in all brain structures analyzed was always higher than in the conscious state for both anesthetics at all MAC levels. One cause of these observations may be that during brain excision after decapitation, 4-iodo-N-methyl-[^{14}C]antipyrine may diffuse rapidly from these small high flow structures into the surrounding areas of low flow, resulting in artificially lowered blood flow values in these structures, which results in an apparently disturbed flow–metabolism coupling. However, this finding should affect all small brain structures with high blood flow values. Because most of these structures showed a well-preserved flow–metabolism coupling, a general diffusion loss of 4-iodo-N-methyl-[^{14}C]antipyrine from small brain structures after decapitation could not be a major cause for the lower flow values obtained in some specific brain structures than predicted from their metabolic rates.

In conclusion, the present investigation shows that sevoflurane and isoflurane induced a decrease in glucose utilization and an increase in blood flow of the brain. These effects are less pronounced for sevoflurane than for isoflurane, resulting in an increase of mean CBF during 2 MAC sevoflurane anesthesia comparable with the increase of mean CBF during 1 MAC isoflurane anesthesia. In addition, the local analysis reveals that LCBF is mainly adjusted to the local metabolic demands at 1 MAC and to a lesser extent at 2 MAC of isoflurane and sevoflurane.

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