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Effects of Xenon on Cerebral Blood Flow and Cerebral Glucose Utilization in Rats

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Background: **The effects of xenon inhalation on mean and local cerebral blood flow (CBF) and mean and local cerebral glucose utilization (CGU) were investigated using iodo-[^{14}C]antipyrine and [^{14}C]deoxyglucose autoradiography.**

Methods: **Rats were randomly assigned to the following groups: conscious controls (n = 12); 30% (n = 12) or 70% xenon (n = 12) for 45 min for the measurement of local CBF and CGU; or 70% xenon for 2 min (n = 6) or 5 min (n = 6) for the measurement of local CBF only.**

Results: **Compared with conscious controls, steady state inhalation of 30 or 70% xenon did not result in changes of either local or mean CBF. However, mean CBF increased by 48 and 37% after 2 and 5 min of 70% xenon short inhalation, which was entirely caused by an increased local CBF in cortical brain regions. Mean CGU determined during steady state 30 or 70% xenon inhalation remained unchanged, although local CGU decreased in 7 (30% xenon) and 18 (70% xenon) of the 40 examined brain regions. The correlation between CBF and CGU in 40 local brain structures was maintained during steady state inhalation of both 30 and 70% xenon inhalation, although at an increased slope at 70% xenon.**

Conclusion: **Effects of 70% xenon inhalation on CBF in rats are time-dependent. During steady state xenon inhalation (45 min), mean values of CBF and CGU do not differ from control values, and the relation of regional CBF to CGU is maintained, although reset at a higher level.**

XENON is an inhalational anesthetic agent with physicochemical characteristics that provide rapid induction[1] and emergence from anesthesia[2,3] because of its four times lower blood gas solubility than nitrous oxide.[4] In humans, a minimal alveolar concentration (MAC) value can be reached during atmospheric conditions (0.71 atm MAC)[5] within approximately 8 min after endotracheal intubation. Xenon is an analgesic and also maintains hemodynamic, myocardial, and neurohumoral stability during anesthesia.[6–10]

Xenon (stable or radiolabeled) has been also used as an inert tracer for measurements of cerebral blood flow (CBF). However, evidence indicates that xenon may itself influence CBF. The concentrations used for the combination of conventional computed tomography with the stable xenon technique for determination of CBF are limited to 40% or less since an autoradiographic study in rats reported a doubled local CBF in some neocortical structures after a 1- and 2-min period of 80% xenon inhalation.[11] These results were confirmed by studies in which microspheres and xenon injection techniques were used.[12–14] In baboons, various concentrations of xenon (35–42%) and periods of inhalation (2–5 min)[12,13] induced increases in CBF by 17–22%, respectively. Increases of CBF in the range of 30% during a 4–5-min inhalation period of 30–35% xenon have also been found in humans.[14]

Although it was known that the equilibration of xenon with white matter needs much longer time periods than those used for diagnostic purposes of computed tomography with xenon,[15] longer exposure times to high concentrations of xenon have not been investigated. With the intended use of xenon in anesthetic care,[16] the long-term effects of high concentrations of xenon on the brain become more interesting.

Therefore, this study compares the steady state effects of 70% xenon inhalation on local CBF with those of short-term inhalation. In addition, the effects of 30 and 70% xenon inhalation on the relation between local CBF and local cerebral glucose utilization (CGU) were measured.

Materials and Methods

Animals

After obtaining approval from the Institutional Animal Care Committee (Regierungspraesidium Karlsruhe, Germany), the experiments were performed on 48 male Sprague-Dawley rats weighing 316 ± 26 g (Charles River Deutschland, Sulzfeld, Germany). Animals were kept under temperature-controlled environmental conditions on a 14:10 light:dark cycle, were fed standard diet (Altromin C 1000; Altromin, Lage, Germany), and were allowed free access to food and water until starting the experiments.

Study Groups and Experimental Protocol

Rats were anesthetized by inhalation of isoflurane (1 MAC) in oxygen–nitrous oxide (fraction of inspired oxygen [F_{IO_2}] = 0.4). Anesthesia was maintained breathing the same gas mixture spontaneously *via* a nose cone. Cannulation of right femoral artery and vein was per-

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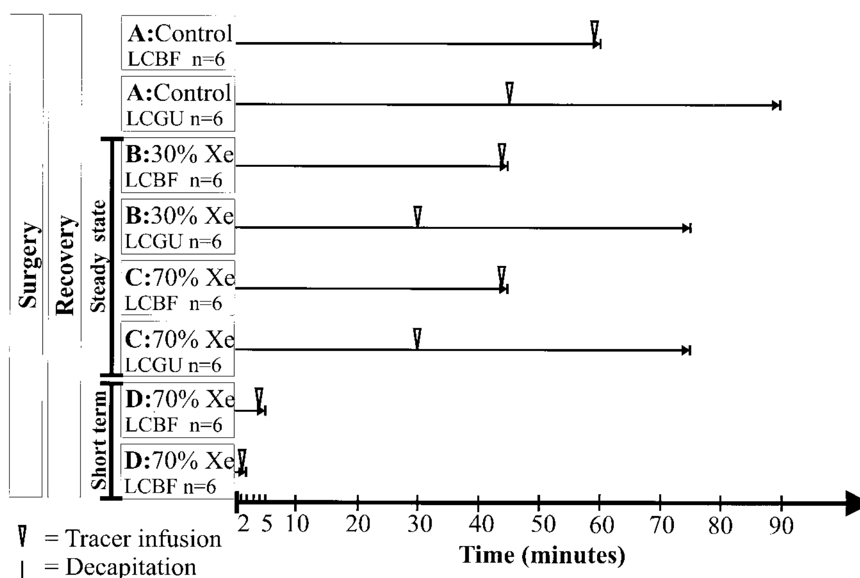

Fig. 1. Experimental gas inhalation. Surgery in all rats lasted for approximately 20 min, with a recovery period of 60 min. (*A–D*) Each box (squares) represents one experimental group. With variation of the xenon concentration (30 and 70%), nitrogen concentration changed from 40% to 0%, while oxygen concentration was kept constant at 30%. In the steady state and control experiments, a various time delay until the end of the cerebral blood flow experiments (1 min) and cerebral glucose utilization experiments (45 min) is required because of the different tracer kinetics in these two methods for the assessment of a physiology at the same time.[18,37] Therefore, to relate the cerebral blood flow measurement to the glucose utilization, the cerebral blood flow experiment was performed 15 min after the deoxyglucose pulse infusion in the respective cerebral glucose utilization experiment. In the short-term inhalation groups, the gas-sealed inhalation chamber was first flushed with 70% xenon for 45 s. The inhalation periods with 70% xenon for 2 or 5 min were then started. For local cerebral blood flow (LCBF) measurements, tracer infusion was started 60 s before decapitation. (*A*) Conscious controls: rats breathed nitrogen–oxygen (F_{IO_2} = 0.3) for 45 or 60 min until either 2-[1-^{14}C]deoxy-D-glucose (measurement of local cerebral glucose utilization [LCGU]) or 4-iodo-*N*-methyl-[^{14}C]antipyrine (measurement of LCBF) was infused, respectively. Tracer infusion for the LCBF experiments began at minute 59, and decapitation was performed at minute 60. Tracer infusion for the LCGU experiments was performed as a pulse at minute 45, and decapitation was performed at minute 90. (*B*) Steady state inhalation of 30% xenon: rats breathed 30% xenon in nitrogen–oxygen (F_{IO_2} = 0.3). After a xenon equilibration period within the rat of 30 min, LCGU experiments were started with a pulse infusion and lasted for another 45 min. LCBF experiments were performed after a xenon equilibration period within the rat of 44 min and lasted for another minute. (*C*) Steady state inhalation of 70% xenon: rats breathed 70% xenon in oxygen (F_{IO_2} = 0.3). Except for the higher xenon concentrations used, the experiments were identical with the steady state inhalation experiments of 30% xenon. (*D*) Short-term inhalation of 70% xenon: in one group, rats breathed 70% xenon in oxygen (F_{IO_2} = 0.3) for 1 min. Then 4-iodo-*N*-methyl-[^{14}C]antipyrine infusion for the measurement of LCBF was started, which lasted for another minute. In the other group of short-term inhalation, rats breathed 70% xenon in oxygen (F_{IO_2} = 0.3) for 4 min, when 4-iodo-*N*-methyl-[^{14}C]antipyrine infusion for the measurement of LCBF was started, which lasted for another minute.

formed using polyethylene catheters (PE-50; Labokron, Sinsheim, Germany). Oxygen saturation was monitored using pulse oximetry (Nonin 8600V Pulse Oximeter, Nonin Medical Inc., Plymouth, MN). After wound closure, animals were placed in tunnels (Braintree Scientific, Boston, MA) for recovery breathing nitrogen–oxygen (F_{IO_2} = 0.3) in a gas-sealed head chamber. Gas within the head chamber was exchanged by a ventilation circuit with a flow of 200 ml/min (Cicero; Draeger AG, Lübeck, Germany). The gas concentrations were monitored by mass spectrometry (Xenotec 2000, Draeger AG). Mean arterial blood pressure and heart rate were registered continuously by a quartz pressure transducer (Hewlett-Packard, Palo Alto, CA). Arterial blood gases were checked in a pH–blood gas analyzer (AVL Gas Check 939; AVL, Graz, Austria). Rectal temperature was controlled between 37°C and 37.5°C with a heating lamp.

After a recovery period of 60 min, all rats were placed in a tunnel where they breathed spontaneously. According to applied gas mixture and the duration of gas administration, rats were randomly assigned to various groups (fig. 1).

Steady state conditions were assumed after 45 min of xenon equilibration within the rat brain because the equilibration time of xenon is 2 min for grey matter and more than 30 min in white matter.[15]

Measurement of Local Cerebral Blood Flow and Local Cerebral Glucose Utilization

With each treatment, six rats were used for the autoradiographic determination of local CBF and six rats for the measurement of local CGU according to previous descriptions.[17,18] In the short inhalation groups, only local CBF experiments could be performed. Comparable local CGU experiments using deoxyglucose were not possible because of the long experimental time (45 min) of this type of experiment.

For the measurement of local CGU, 125 μCi/kg body weight of 2-[1-^{14}C]deoxy-D-glucose (specific activity, 50–56 mCi/mmol; New England Nuclear, Dreieich, Ger-

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many) were injected as a pulse *via* the femoral venous catheter within 20 s after a period of 30-min steady state inhalation of the respective gas concentration. Timed arterial blood samples of 80 μl were collected through the arterial catheter at 15, 30, and 45 s and at 1, 2, 3, 5, 7.5, 10, 15, 25, 35, and 45 min. The blood samples were immediately centrifuged and stored on ice until assays for plasma 2-[1-^{14}C]deoxy-D-glucose and glucose concentrations were performed. Immediately after the final arterial blood sample was collected, the animal was decapitated, and the brain was rapidly removed and frozen in isopentane chilled to −60°C.

For the measurement of local CBF, after various inhalation periods in the respective groups, 100 μCi/kg body weight of 4-iodo[N-methyl-^{14}C]antipyrine (specific activity, 54 mCi/mmol; Amersham-Buchler, Braunschweig, Germany) 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 previously,[17] 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 (1.3 cm in diameter) that had been prepared in small plastic beakers and weighed. The samples were weighed, and radioactivity was estimated with a liquid scintillation counter (TriCarb 4000 series; Canberra Packard, Frankfurt, Germany) after extraction of the radioactive compound with ethanol. After the 1-min infusion and sampling, the animal was decapitated. The brain was removed as quickly as possible and frozen in isopentane chilled to −60°C. In both the 2-[1-^{14}C]deoxy-D-glucose and 4-iodo[*N*-methyl-^{14}C]antipyrine experiments, the frozen brains were coated with chilled embedding medium (Lipshaw, Detroit, MI), stored at −80°C in plastic bags, sectioned in 20-μm sections at −20°C in a cryostat, and autoradiographed along with precalibrated [^{14}C]methyl methacrylate standards.

Local tissue concentrations of [^{14}C] were determined from the autoradiographs by densitometric analysis. Local CGU and CBF were calculated from the local concentrations of [^{14}C] and the time courses of the plasma [^{14}C]deoxyglucose and iodo[^{14}C]antipyrine concentrations, including corrections for the lag and washout in the arterial catheter. The washout correction rate constant was 100/min, and the brain–blood partition coefficient for iodo[^{14}C]antipyrine was 0.9 in our rats.

Autoradiographic images were converted to digitized optical density images by an image processing system (MCID; Imaging Research, St. Catharines, Canada). For measurements of separate brain structures, an ellipsoid cursor was used and adjusted to the size of the individual region. For both measurement of mean CBF and mean

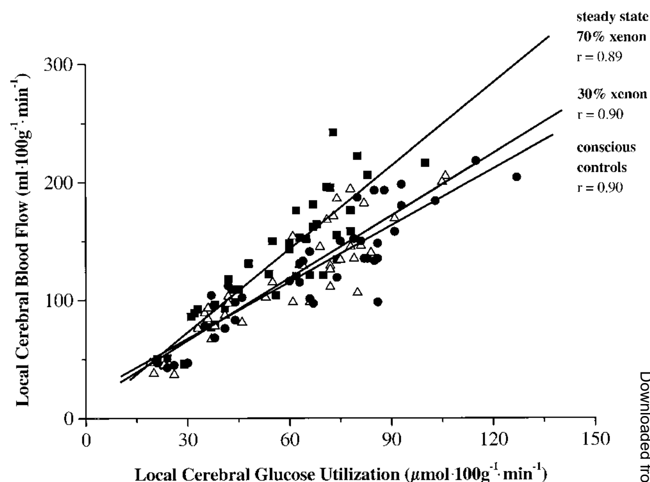

Fig. 2. Relation between local cerebral glucose utilization and local cerebral blood flow. Conscious controls (circles), 30% xenon inhalation (triangles), 70% xenon inhalation (squares). For each of the examined 40 brain structures, the mean of the values of local cerebral blood flow is plotted against the mean of the values of local cerebral glucose utilization. The regression lines were calculated according to y = ax + b, with y being local cerebral blood flow and x being local cerebral glucose utilization. Control group: y = 1.6x + 19, r = 0.90; 30% xenon inhalation: y = 1.8x + 13, r = 0.90; and 70% xenon inhalation: y = 2.3x + 2, r = 0.89 (*P* < 0.05 between the slopes of all groups).

CGU, the area and optical density of the whole coronal sections were analyzed from sections of the whole brain selected every 200 μm. As a result, the area-weighted means of all measured sections throughout the rat brain were obtained.

Statistical Analysis

Two kinds of analysis were performed: (1) for testing of the effects of different concentrations of xenon on glucose utilization during steady state conditions, glucose utilization and physiologic variables were compared between a control group and two groups of steady state inhalation of either 30 or 70% xenon; (2) for testing the effects of 70% xenon inhalation on CBF, values of CBF and physiologic variables were compared between a control group (no inhalation of xenon) and three groups of 2 min, 5 min, and steady state (45 min) inhalation of 70% xenon.

Data were evaluated by analysis of variance, and differences between the experimental groups were investigated by *t* tests for multiple comparisons with Bonferroni correction.[19] Data are presented as mean ± SD. The level of statistical significance was set at 0.05. The overall relation between local CGU and local CBF in the examined structures of the brain (fig. 2) was assessed by the least-squares fit of the data to y = ax + b, where x is the mean local CGU in a given region, and y is the mean local CBF in that same area. Contrasts of slopes of the local CBF–CGU regression lines were tested by common *t* test statistics with Bonferroni correction for multiple comparisons. Because of the limitations of this kind of

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Table 1. Physiologic Variables

	Conscious Controls	30% Xenon Inhalation	70% Xenon Inhalation		
		45 min	2 min	5 min	45 min
Arterial pH	7.38 ± 0.02	7.36 ± 0.04	7.34 ± 0.03	7.34 ± 0.04	7.36 ± 0.06
Pa_{O_2} (mmHg)	157 ± 23	144 ± 17	144 ± 22	161 ± 27	150 ± 19
Pa_{CO_2} (mmHg)	41 ± 4	42 ± 3	46 ± 3*	47 ± 3*†	42 ± 4‡
Plasma glucose concentration (mg/dl)	177 ± 54	177 ± 42§	190 ± 39*‡‖	152 ± 90§	165 ± 44
Hematocrit (%)	44 ± 2	45 ± 2	45 ± 1	44 ± 2	45 ± 2
Mean arterial pressure (mmHg)	117 ± 8	117 ± 4	120 ± 8	111 ± 10	112 ± 7
Heart rate (beats/min)	325 ± 45	308 ± 16§	384 ± 44*‖	435 ± 40*†	299 ± 27‡

Values are mean ± SD. Conscious controls breathed 30% O_2 and 70% N_2. Animals in the 30% xenon group breathed 30% xenon, 30% O_2, and 40% N_2. Animals in the 70% xenon group breathed 70% xenon and 30% O_2.

* $P < 0.05$ *versus* conscious controls. † $P < 0.05$ *versus* 70% xenon, 45 min. ‡ $P < 0.05$ *versus* 70% xenon, 5 min. § $P < 0.05$ *versus* 70% xenon, 2 min. ‖ $P < 0.05$ *versus* 30% xenon, 45 min.

Pa_{O_2} = arterial oxygen tension; Pa_{CO_2} = arterial carbon dioxide tension.

analysis, an additional, more rigorous statistical approach using log-transformed data was applied, examining the relation of local CBF and local CGU by a repeated measure of the analysis of variance according to McCulloch *et al.*[20] and Ford *et al.*[21] For this analysis, a computer software package (BMDP2v; BMDP Statistical Software Inc., Los Angeles, CA) considering interanimal variability and enabling the detection of heterogeneities in the relation between local CGU and CBF was used.

Results

Steady state inhalation of xenon did not result in changes of the physiologic variables at any concentration tested (table 1). During inhalation of 70% xenon for 2 and 5 min, changes of arterial carbon dioxide tension, plasma glucose levels, and heart rate were found.

Mean CBF values during 30 or 70% steady state inhalation of xenon were not different from conscious control values (fig. 3). Local CBF remained unchanged in all structures tested during steady state inhalation of 30 and 70% xenon (table 2).

During 2- and 5-min inhalation of 70% xenon, however, mean CBF increased by 48 and 37% compared with conscious controls, respectively (fig. 3). Analysis of the various loci (table 2) showed that this increase in mean CBF was caused by a large increase in local CBF in all cerebral cortical structures (pyriform, frontal, sensory motor, parietal, cingulate, auditory, and visual cortex). In contrast to these local CBF increases, local CBF was decreased after 2-min (by 32%) or 5-min inhalation (by 36%) in the cerebellar cortex during 70% xenon inhalation.

Mean CGU did not change during 30% (54 ± 5 μmol · 100 g^{-1} · min^{-1}) or 70% xenon inhalation (49 ± 2 μmol · 100 g^{-1} · min^{-1}) compared with the conscious control group (54 ± 5 μmol · 100 g^{-1} · min^{-1}). Values of local CGU are shown in table 3. Compared with controls, inhalation of 30 and 70% xenon induced significant decreases in local CGU in 7 and 18 of the 40 examined brain regions, respectively.

The relation between local CGU and CBF at steady state exposure to xenon is plotted in figure 2. Close correlations were found between local CGU and CBF for control conditions ($r = 0.90$; $P < 0.05$), 30% xenon ($r = 0.94$; $P < 0.05$), and 70% xenon ($r = 0.89$; $P < 0.05$). As revealed from the analysis of log-transformed data previously mentioned,[20] the slopes of the regression lines were not significantly different between controls (1.6 ml/μmol; $P > 0.05$) and 30% xenon (1.8 ml/μmol; $P > 0.05$), but both were different from 70% xenon (2.4 ml/μmol; $P \leq 0.001$).

Discussion

The data obtained show that steady state inhalation of 30 or 70% xenon did not result in changes of mean or local CBF or mean CGU, whereas local CGU was decreased in 7 by 30% xenon and 18 of the 40 brain structures by 70% xenon. In contrast to these moderate effects at steady state, mean CBF was considerably increased during the first 5 min of inhalation of 70% xenon. This increase was caused by an increase in local CBF in most cortical brain structures. The correlation between local CBF and local GCU that existed during control conditions was maintained during steady state inhalation of both 30 and 70% xenon, although at an increased slope at 70% xenon.

The most important result of this investigation is that steady state inhalation of 70% xenon does not result in an increase in CBF as had been expected on the basis of several previous results.[11,12] However, in these previous studies, short inhalation periods of less than 5 min were used. Because at that time xenon was only used for xenon computed tomography during short exposure times and in low concentrations because of its high costs, long-term effects of xenon were of little interest. The situation has now changed. Xenon anesthesia is in phase III clinical studies, and the costs can be reduced by recycling techniques. With the intended use of xenon in high concentrations for anesthesia, interest in the

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Table 2. Local Cerebral Blood Flow of the Experimental Groups

	Conscious Controls	Steady State 30% Xenon Inhalation	2 min 70% Xenon Inhalation	5 min 70% Xenon Inhalation	Steady State 70% Xenon Inhalation
Cerebellum					
Cerebellar cortex	117 ± 15	106 ± 12†	79 ± 17*	75 ± 12*‡	102 ± 15
Dentate nuclei	203 ± 61	190 ± 25	213 ± 43	197 ± 24	219 ± 24
Medulla–pons					
Vestibular nucleus	198 ± 88	176 ± 12	170 ± 21	163 ± 21	181 ± 28
Cochlear nucleus	244 ± 97	185 ± 31	219 ± 67	222 ± 40	234 ± 30
Superior olive	221 ± 71	184 ± 23	190 ± 43	174 ± 10	197 ± 29
Pontine gray	105 ± 12	95 ± 7†§‖	120 ± 12‡	115 ± 13‡	113 ± 6‡
Lateral lemniscus	189 ± 48	158 ± 19	149 ± 25	144 ± 17*	171 ± 16
Mesencephalon					
Inferior colliculus	240 ± 103	200 ± 32	170 ± 32	184 ± 11	212 ± 13
Superior colliculus	132 ± 24	130 ± 19†	146 ± 20	169 ± 28*‡	158 ± 11
Substantia nigra CP	112 ± 15	111 ± 22	104 ± 10	117 ± 9	119 ± 13
Substantia nigra RP	83 ± 11	81 ± 17	59 ± 8*‖	75 ± 15	87 ± 12§
Diencephalon					
Medial geniculate body	190 ± 61	169 ± 32	166 ± 15	177 ± 16	206 ± 42
Lateral geniculate body	134 ± 22	145 ± 37	167 ± 36	182 ± 22*	162 ± 26
Mammillary body	151 ± 48	134 ± 22	129 ± 16	147 ± 27	134 ± 21
Hypothalamus	101 ± 25	89 ± 10	82 ± 6	83 ± 13	89 ± 10
Ventral thalamus	141 ± 28	130 ± 22	165 ± 13	146 ± 28	143 ± 14
Lateral thalamus	152 ± 33	145 ± 26	156 ± 17	151 ± 17	164 ± 24
Telencephalon					
Hippocampus CA1	99 ± 14	98 ± 19†	125 ± 11	128 ± 25*‡	104 ± 16
Hippocampus CA2	77 ± 12	80 ± 16	98 ± 14	103 ± 16*	97 ± 16
Hippocampus CA3	101 ± 17	97 ± 20	86 ± 20	98 ± 18	110 ± 9
Hippocampus CA4	101 ± 17	96 ± 23	103 ± 14	114 ± 13	117 ± 8
Dentate gyrus	85 ± 14	84 ± 20	65 ± 9‖	74 ± 11	96 ± 6§
Amygdaloid complex	91 ± 17	84 ± 10	106 ± 15	95 ± 17	86 ± 9
Globus pallidus	67 ± 9	67 ± 5†	77 ± 5	89 ± 18*‡	77 ± 11
Caudate nucleus	116 ± 19	111 ± 13†	161 ± 31*‖	177 ± 29*‡	121 ± 10§
Nucleus accumbens	115 ± 18	102 ± 12	146 ± 28	133 ± 32	131 ± 17
Visual cortex	142 ± 26	144 ± 20†	292 ± 70*†‖	220 ± 29*‡§	160 ± 21§
Auditory cortex	149 ± 35	139 ± 21†	305 ± 57*‖	249 ± 55*‡	174 ± 23§
Parietal cortex	137 ± 33	126 ± 22†	293 ± 34*†‖	233 ± 43*‡§	153 ± 17§
Sensory motor cortex	132 ± 26	129 ± 14†	265 ± 54*‖	206 ± 66*‡	152 ± 27§
Frontal cortex	131 ± 36	126 ± 17†	245 ± 40*‖	227 ± 68*‡	148 ± 21§
Cingulate cortex	140 ± 22	146 ± 27†	323 ± 44*‖	306 ± 37*‡	195 ± 40§
Pyriform cortex	98 ± 12	106 ± 11†	170 ± 20*‖	183 ± 30*‡	121 ± 16§
Lateral septal nuclei	98 ± 15	87 ± 15	105 ± 12	101 ± 15	94 ± 11
Myelinated fiber tracts					
Internal capsule	46 ± 7	45 ± 6	45 ± 10	47 ± 7	45 ± 7
Medial habenulae	155 ± 36	154 ± 38	131 ± 13	145 ± 17	150 ± 33
Lateral habenulae	179 ± 44	186 ± 19	160 ± 31	178 ± 30	181 ± 37
Corpus callosum	45 ± 14	37 ± 12	46 ± 12	42 ± 9	46 ± 9
Genu of corpus callosum	46 ± 9	38 ± 5	54 ± 7	51 ± 13	50 ± 9
Cerebellar white matter	48 ± 11	54 ± 9†	42 ± 8	39 ± 9‡	54 ± 8

Values are $ml \cdot 100\ g^{-1} \cdot min^{-1}$, mean ± SD. Conscious controls breathed 30% O_2 and 70% N_2. Animals in the 30% xenon group breathed 30% xenon, 30% O_2, and 40% N_2. Animals in the 70% xenon group breathed 70% xenon and 30% O_2.

* $P < 0.05$ *versus* conscious controls. † $P < 0.05$ *versus* 70% xenon, 5 min. ‡ $P < 0.05$ *versus* 30% xenon, 45 min. § $P < 0.05$ *versus* 70% xenon, 2 min. ‖ $P < 0.05$ *versus* 70% xenon, 45 min.

CP = compact part; RP = reticular part; steady state xenon inhalation = 45 min.

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effects of long exposure times of xenon on CBF is growing. In concert with our results of steady state inhalation, a recently published study in pigs used a ventilation period of 30 min and failed to show any effect of various doses of xenon in propofol-sedated pigs on regional blood flow measured by the sagittal sinus outflow technique.[22] Moreover, the time dependency of the xenon effect on CBF is known from a previous investigation.[13] Hartmann *et al.*[13] reported that an adaptation of xenon-induced initial increases in CBF exists. Using the intra-arterial xenon-133 method for the measurement of local CBF in baboons, the adaptation of an initially increased CBF after the first 4 min occurred during the continuous inhalation of 35% xenon for 45 min to the baseline CBF. Our study using autoradiographic CBF determination now might further support the report of a reversal of initial xenon-induced increase of CBF because after steady state inhalation of 70% xenon for a 45-min period, no differences in mean CBF and mean CGU were detected.

Table 3. Local Cerebral Glucose Utilization of the Experimental Groups

	Conscious Controls	Steady State 30% Xenon Inhalation	Steady State 70% Xenon Inhalation
Cerebellum			
Cerebellar cortex	43 ± 3	36 ± 5*	33 ± 1*
Dentate nuclei	85 ± 15	78 ± 6	80 ± 10
Medulla–pons			
Vestibular nucleus	93 ± 11	73 ± 9*	62 ± 11*
Cochlear nucleus	115 ± 12	105 ± 16†	73 ± 25*‡
Superior olive	93 ± 11	82 ± 18	71 ± 13*
Pontine gray	42 ± 4	42 ± 4	42 ± 5
Lateral lemniscus	80 ± 11	71 ± 9	62 ± 6*
Mesencephalon			
Inferior colliculus	127 ± 20	106 ± 22	100 ± 11*
Superior colliculus	63 ± 8	64 ± 6	78 ± 19
Substantia nigra CP	60 ± 8	55 ± 9	54 ± 7
Substantia nigra RP	35 ± 8	33 ± 5	38 ± 7
Diencephalon			
Medial geniculate body	88 ± 13	91 ± 8	83 ± 11
Lateral geniculate body	64 ± 11	69 ± 10	67 ± 11
Mammillary body	75 ± 8	75 ± 12	74 ± 10
Hypothalamus	37 ± 5	35 ± 3	32 ± 5
Ventral thalamus	66 ± 8	63 ± 4	60 ± 3
Lateral thalamus	79 ± 8	78 ± 9	68 ± 5*
Telencephalon			
Hippocampus CA1	67 ± 12	61 ± 7	56 ± 6
Hippocampus CA2	41 ± 11	38 ± 4	38 ± 7
Hippocampus CA3	46 ± 6	42 ± 5	45 ± 4
Hippocampus CA4	66 ± 9	66 ± 7	62 ± 8
Dentate gyrus	44 ± 9	46 ± 7	41 ± 5
Amygdaloid complex	38 ± 5	36 ± 3	31 ± 3*
Globus pallidus	38 ± 7	37 ± 3	37 ± 5
Caudate nucleus	74 ± 5	72 ± 10	70 ± 5
Nucleus accumbens	66 ± 7	53 ± 10	48 ± 10*
Visual cortex	85 ± 7	79 ± 11	74 ± 4*
Auditory cortex	91 ± 7	84 ± 13	78 ± 8
Parietal cortex	82 ± 7	72 ± 7*	63 ± 7*
Sensory motor cortex	83 ± 7	72 ± 8*	65 ± 7*
Frontal cortex	86 ± 14	72 ± 9*	60 ± 4*
Cingulate cortex	86 ± 9	81 ± 10	72 ± 6*
Pyriform cortex	86 ± 10	80 ± 5†	66 ± 9*‡
Lateral septal nuclei	44 ± 5	41 ± 4	37 ± 5*
Myelinated fiber tracts			
Internal capsule	26 ± 6	23 ± 5	23 ± 5
Medial habenulae	81 ± 16	61 ± 9*	55 ± 8*
Lateral habenulae	103 ± 10	74 ± 7*	67 ± 13*
Corpus callosum	30 ± 6	26 ± 5	29 ± 4
Genu of corpus callosum	21 ± 6	20 ± 3	21 ± 3
Cerebellar white matter	24 ± 6	19 ± 3	24 ± 6

Values are $\mu mol \cdot 100\ g^{-1} \cdot min^{-1}$, mean ± SD. Conscious controls breathed 30% O_2 and 70% N_2. Animals in the 30% xenon group breathed 30% xenon, 30% O_2, and 40% N_2. Animals in the 70% xenon group breathed 70% xenon and 30% O_2.

* $P < 0.05$ *versus* conscious controls. † $P < 0.05$ *versus* 70% xenon group. ‡ $P < 0.05$ *versus* 30% xenon group.

CP = compact part; RP = reticular part; steady state xenon inhalation = 90 min.

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We were unable to detect the origin of the cortical increases in CBF. The cause of these changes remains unknown. Several possibilities exist that might explain the effects, such as an increase in arterial carbon dioxide partial pressure (Pa_{CO_2}), neuro-excitation, or dilation of cerebral vessels by xenon. Each of these possibilities are considered in the following paragraphs, although other possibilities cannot be excluded.

First, an increased Pa_{CO_2} must be considered as a cause of the increased CBF during the first minutes of the inhalation because Pa_{CO_2} was increased by 4 mmHg (70% xenon, 2 min) and 5 mmHg (70% xenon, 5 min). Such an increase in Pa_{CO_2} should induce a general increase in CBF by 10–15% according to previous studies of our group.[23] Therefore, the general increase in CBF by 28 and 17% as measured in the present study during 2- and 5-min 70% xenon inhalation could be well explained by the increase in Pa_{CO_2}. However, the increase in Pa_{CO_2} cannot be the cause of large increase in neocortical CBF by 97 and 63% as found in the present study. With respect to the specific cortical effects, this interpretation is consistent with previous results of Junck *et al.*[11] Dur-

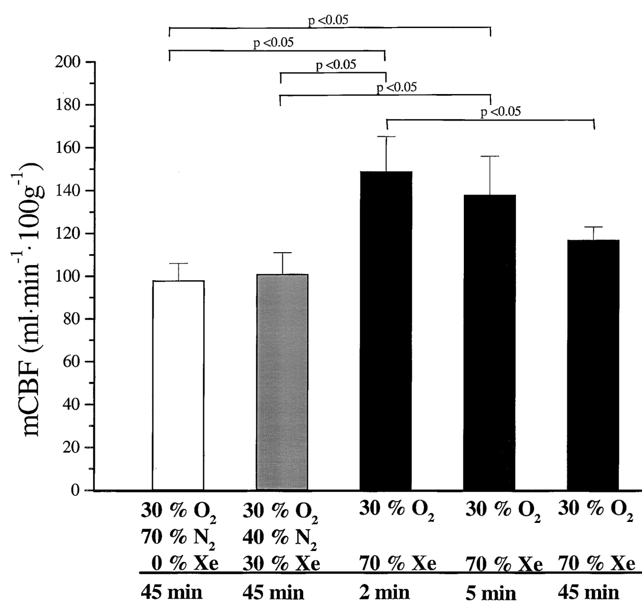

Fig. 3. Time dependency of the effect of xenon inhalation on mean cerebral blood flow (mCBF).

ing 1- and 2-min inhalation of 80% xenon, the investigators found a small increase in Pa_{CO_2} of less than 2 mmHg but a large increase in neocortical local CBF by 75 and 96%, respectively.

Second, neuro-excitation could be the cause of the observed increase in CBF during short-term inhalation of 70% xenon. The increase in CBF could be either secondary to an increase in brain activity at the onset of xenon inhalation or directly caused by an activation of specific neuronal receptors by xenon. An increase in brain activity could be concomitant to an enhanced innervation of respiratory muscles to meet the increased respiratory work during the inhalation of xenon because 70% xenon has a 4.6-fold higher specific weight than air.[24] The increased CBF would then reflect the enhanced activity of neurons that activate the efferent tracts to respiratory muscles. An activation of specific receptors by xenon appears possible because xenon induces inhibition of excitatory *N*-methyl-D-aspartate receptors in contrast to the activation of inhibitory γ-aminobutyric acid type A receptors by the majority of other general anesthetics.[25] Direct neuro-excitatory effects of xenon should be reflected in changes in local CGU in brain regions where these receptors are localized. However, because the [^{14}C]deoxyglucose method requires stable experimental conditions over 45 min, local CGU could not be measured in the short-term inhalation groups during the present investigation. Therefore, neuro-excitation could not be demonstrated or excluded as a cause for the increase in local CBF observed in the present study during the first minutes of 70% xenon inhalation.

Third, the most likely cause of the observed initial increase in CBF in the short-term inhalation groups is a direct vasodilator action of xenon that wanes within the next 45 min. During 2-min inhalation of 70% xenon, local CBF was doubled in neocortical brain structures (frontal, sensory motor, parietal, auditory cortex) from 137 ± 8 to 277 ± 27 ml $\cdot$ 100 g^{-1} $\cdot$ min^{-1}. After 45 min, CBF had returned to preinhalation levels. An initial marked increase in CBF that showed a tendency to decrease with time has also been described for nitrous oxide[26] and halothane.[27–29] During 1 h of 70% inhalation of nitrous oxide in goats, Pelligrino *et al.*[26] observed an increase in CBF that was mainly restricted to cortical brain structures. The maximum increase of 65% compared with controls was found at 15 min, and an increase of 43% was still found after 60 min.[26] As to halothane, CBF was nearly doubled in goats within 4 min after start of 1% halothane anesthesia and returned to preanesthetic levels after 2.5 h.[28] Likewise, 5 min after start of inhalation in dogs, 1.33% halothane induced an increase in CBF by 79%. During continuous inhalation, CBF then decreased at a rate of 8.7% per hour.[29] Compared with the effects of nitrous oxide and halothane, the dilating effects of xenon were restricted to cortical regions, less prominent for the mean CBF (maximum increase of 48%) and below detection after 45 min. The cause of the observed initial increases in CBF by xenon, nitrous oxide, and halothane are unclear as well as the mechanism of adaptation of CBF during longer inhalation periods.

Steady state inhalation of xenon produced a metabolic depression pattern only present at the higher concentration (70%) and located mainly in the cerebral cortex. A predominant suppression of cortical metabolism has already been described for the halogenated ethers isoflurane, sevoflurane, and desflurane.[30–32] At a concentration sufficient to induce anesthesia (1 MAC), these anesthetics induce a reduction of mean CGU in conscious rats by 43, 34, and 52%, respectively. In contrast, we were not able to demonstrate a reduction of mean CGU even by high concentrations of xenon. This may be caused by the failure to attain a xenon concentration of 1 MAC at atmospheric pressure because a pressure of 1.61 ± 0.17 atm is necessary to obtain 1 MAC xenon concentration in rats.[5] In addition, because of the rather small number of experimental animals used for the experiment, it cannot be ruled out that a small reduction of mean CGU might have occurred that could not be detected statistically.

The physiologic relation between the cerebral blood of cerebral glucose metabolism to blood flow is varied by other volatile anesthetics as previously shown.[31,33–35] However, the shift of the relation to higher levels (2.4 ml/μmol) is in the level of 1 MAC isoflurane and sevoflurane (2.5 to 2.6 and 2.3 ml/μmol)[36] but less than the one of desflurane at 1 MAC (3.5 ml/μmol).[34] Based on minor effects of 0.5 MAC xenon on the cerebral metabolism, this suggests the presence of a homogenous flow increase in the majority of structures even if the

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increases in mean and local CBF did not reach the level of significance.

In conclusion, during the first minutes of xenon inhalation, mean CBF is increased by a maximum of approximately 50%. The cause of the transient initial vasodilation might be either a direct vascular action of xenon or an indirect effect mediated by a xenon-induced metabolic stimulation. During steady state inhalation of 70% xenon, changes of cerebral metabolism and CBF were not detected. Because of local changes in blood flow and metabolism, the coupling of local CBF to local CGU is reset but shifted to a higher level as already known from other inhalational anesthetics.

References

1. Nakata Y, Goto T, Morita S: Comparison of inhalation inductions with xenon and sevoflurane. Acta Anaesthesiol Scand 1997; 41:1157–61
2. Goto T, Saito H, Nakata Y, Uezono S, Ichinose F, Morita S: Emergence times from xenon anaesthesia are independent of the duration of anaesthesia. Br J Anaesth 1997; 79:595–9
3. Goto T, Saito H, Shinkai M, Nakata Y, Ichinose F, Morita S: Xenon provides faster emergence from anesthesia than does nitrous oxide–sevoflurane or nitrous oxide–isoflurane. Anesthesiology 1997; 86:1273–8
4. Goto T, Suwa K, Uezono S, Ichinose F, Uchiyama M, Morita S: The blood-gas partition coefficient of xenon may be lower than generally accepted. Br J Anaesth 1998; 80:255–6
5. Koblin DD, Fang Z, Eger EI 2nd, Laster MJ, Gong D, Ionescu P, Halsey MJ, Trudell JR: Minimum alveolar concentrations of noble gases, nitrogen, and sulfur hexafluoride in rats: Helium and neon as nonimmobilizers (nonanesthetics). Anesth Analg 1998; 87:419–24
6. Boomsma F, Rupreht J, Man in 't Veld AJ, de Jong FH, Dzoljic M, Lachmann B: Haemodynamic and neurohumoral effects of xenon anaesthesia: A comparison with nitrous oxide. Anaesthesia 1990; 45:273–8
7. Stowe DF, Rehmert GC, Kwok WM, Weigt HU, Georgieff M, Bosnjak ZJ: Xenon does not alter cardiac function or major cation currents in isolated guinea pig hearts or myocytes. Anesthesiology 2000; 92:516–22
8. Lachmann B, Armbruster S, Schairer W, Landstra M, Trouwborst A, Van Daal GJ, Kusuma A, Erdmann W: Safety and efficacy of xenon in routine use as an inhalational anaesthetic. Lancet 1990; 335:1413–5
9. Luttropp HH, Romner B, Perhag L, Eskilsson J, Fredriksen S, Werner O: Left ventricular performance and cerebral haemodynamics during xenon anaesthesia: A transoesophageal echocardiography and transcranial Doppler sonography study. Anaesthesia 1993; 48:1045–9
10. Marx T, Froeba G, Wagner D, Baeder S, Goertz A, Georgieff M: Effects on haemodynamics and catecholamine release of xenon anaesthesia compared with total i.v. anaesthesia in the pig. Br J Anaesth 1997; 78:326–7
11. Junck L, Dhawan V, Thaler HT, Rottenberg DA: Effects of xenon and krypton on regional cerebral blood flow in the rat. J Cereb Blood Flow Metab 1985; 5:126–32
12. Gur D, Yonas H, Jackson DL, Wolfson SK Jr, Rockette H, Good WF, Maitz GS, Cook EE, Arena VC: Measurement of cerebral blood flow during xenon inhalation as measured by the microspheres method. Stroke 1985; 16:871–4
13. Hartmann A, Wassman H, Czernicki Z, Dettmers C, Schumacher HW, Tsuda Y: Effect of stable xenon in room air on regional cerebral blood flow and electroencephalogram in normal baboons. Stroke 1987; 18:643–8
14. Obrist WD, Jaggi JL, Harel D, Smith DS: Effect of stable xenon inhalation on human CBF. J Cereb Blood Flow Metab 1985; 5:S557–8
15. Fatouros PP, Wist AO, Kishore PR, DeWitt DS, Hall JA, Keenan RL, Stewart LM, Marmarou A, Choi SC, Kontos HA: Xenon/computed tomography cerebral blood flow measurements: Methods and accuracy. Invest Radiol 1987; 22:705–12
16. Lynch C 3rd, Baum J, Tenbrinck R: Xenon anesthesia. Anesthesiology 2000; 92:865–8
17. Sakurada O, Kennedy C, Jehle J, Brown JD, Carbin GL, Sokoloff L: Measurement of local cerebral blood flow with iodo [^{14}C] antipyrine. Am J Physiol 1978; 234:H59–66
18. Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M: The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem 1977; 28:897–916
19. Wallenstein S, Zucker CL, Fleiss JL: Some statistical methods useful in circulation research. Circ Res 1980; 47:1–9
20. McCulloch J, Kelly PA, Ford I: Effect of apomorphine on the relationship between local cerebral glucose utilization and local cerebral blood flow (with an appendix on its statistical analysis). J Cereb Blood Flow Metab 1982; 2:487–99
21. Ford I, McColl JH, McCormack AG, McCrory SJ: Statistical issues in the analysis of neuroimages. J Cereb Blood Flow Metab 1991; 11:A89–95
22. Fink H, Blobner M, Bogdanski R, Hanel F, Werner C, Kochs E: Effects of xenon on cerebral blood flow and autoregulation: An experimental study in pigs. Br J Anaesth 2000; 84:221–5
23. Gobel U, Klein B, Schrock H, Kuschinsky W: Lack of capillary recruitment in the brains of awake rats during hypercapnia. J Cereb Blood Flow Metab 1989; 9:491–9
24. Goto T, Saito H, Nakata Y, Uezono S, Ichinose F, Uchiyama M, Morita S: Effects of xenon on the performance of various respiratory flowmeters. Anesthesiology 1999; 90:555–63
25. Franks NP, Dickinson R, de Sousa SL, Hall AC, Lieb WR: How does xenon produce anaesthesia? Nature 1998; 396:324
26. Pelligrino DA, Miletich DJ, Hoffman WE, Albrecht RF: Nitrous oxide markedly increases cerebral cortical metabolic rate and blood flow in the goat. Anesthesiology 1984; 60:405–12
27. Albrecht RF, Miletich DJ, Rosenberg R, Zahed B: Cerebral blood flow and metabolic changes from induction to onset of anesthesia with halothane or pentobarbital. Anesthesiology 1977; 47:252–6
28. Albrecht RF, Miletich DJ, Madala LR: Normalization of cerebral blood flow during prolonged halothane anesthesia. Anesthesiology 1983; 58:26–31
29. Smith AL: The mechanism of cerebral vasodilation by halothane. Anesthesiology 1973; 39:581–7
30. Lenz C, Frietsch T, Fuetterer C, Kuschinsky W, Waschke KF: Local cerebral blood flow, local cerebral glucose utilization, and flow- metabolism coupling during desflurane versus isoflurane anesthesia in rats. Anesthesiology 1999; 91:1720–3
31. Lenz C, Rebel A, van Ackern K, Kuschinsky W, Waschke KF: Local cerebral blood flow, local cerebral glucose utilization, and flow-metabolism coupling during sevoflurane versus isoflurane anesthesia in rats. Anesthesiology 1998; 89:1480–8
32. Hansen TD, Warner DS, Todd MM, Vust LJ: Effects of nitrous oxide and volatile anaesthetics on cerebral blood flow. Br J Anaesth 1989; 63:290–5
33. Maekawa T, Tommasino C, Shapiro HM, Keifer-Goodman J, Kohlenberger RW: Local cerebral blood flow and glucose utilization during isoflurane anesthesia in the rat. Anesthesiology 1986; 65:144–51
34. Lenz C, Frietsch T, Fuetterer C, Rebel A, Kuschinsky W, Waschke KF: Local coupling of cerebral blood flow to cerebral glucose metabolism during inhalational anesthesia in rats: Desflurane versus isoflurane. Anesthesiology 1999; 91:1720–3
35. Hansen TD, Warner DS, Todd MM, Vust LJ: The role of cerebral metabolism in determining the local cerebral blood flow effects of volatile anesthetics: Evidence for persistent flow-metabolism coupling. J Cereb Blood Flow Metab 1989; 9:323–8
36. Lenz C, Rebel A, van Ackern K, Kuschinsky W, Waschke KF: Local cerebral blood flow, local cerebral glucose utilization, and flow- metabolism coupling during sevoflurane versus isoflurane anesthesia in rats. Anesthesiology 1998; 89:1480–8
37. Redies C, Gjedde A: Double-label and conventional deoxyglucose methods: A practical guide for the user. Cerebrovasc Brain Metab Rev 1989; 1:319–67

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