

Local Coupling of Cerebral Blood Flow to Cerebral Glucose Metabolism during Inhalational Anesthesia in Rats

Desflurane versus Isoflurane

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Background: It is not known whether the effects of desflurane on local cerebral glucose utilization (LCGU) and local cerebral blood flow (LCBF) are different from those of other volatile anesthetics.

Methods: Using the autoradiographic iodoantipyrine and deoxyglucose methods, LCGU, LCBF, and their overall means were

measured in 60 Sprague-Dawley rats (10 groups, n = 6 each) during desflurane and isoflurane anesthesia and in conscious controls.

Results: During anesthesia, mean cerebral glucose utilization was decreased compared with conscious controls: 1 minimum alveolar concentration (MAC) desflurane: -52%; 1 MAC isoflurane: -44%; 2 MAC desflurane: -62%; and 2 MAC isoflurane: -60%. Local analysis showed a reduction of LCGU in the majority of the 40 brain regions analyzed. Mean cerebral blood flow was increased: 1 MAC desflurane: +40%; 1 MAC isoflurane: +43%; 2 MAC desflurane and 2 MAC isoflurane: +70%. LCBF was increased in all brain structures investigated except in the auditory cortex. No significant differences ($P < 0.05$) could be observed between both anesthetics for mean values of cerebral glucose use and blood flow. Correlation coefficients obtained for the relation between LCGU and LCBF were as follows: controls: 0.95; 1 MAC desflurane: 0.89; 2 MAC desflurane: 0.60; 1 MAC isoflurane: 0.87; and 2 MAC isoflurane: 0.68.

Conclusion: Differences in the physicochemical properties of desflurane compared with isoflurane are not associated with major differences in the effects of both volatile anesthetics on cerebral glucose utilization, blood flow, and the coupling between LCBF and LCGU. (Key words: Animals; autoradiography; brain; volatile anesthetics.)

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Received from the Department of Anesthesiology and Critical Care Medicine, Faculty for Clinical Medicine Mannheim, University of Heidelberg, Mannheim, Germany. Submitted for publication November 30, 1998. Accepted for publication June 8, 1999. Supported by a grant from Pharmacia & Upjohn, Erlangen, Germany. Presented in part at the Deutscher Anesthesiekongress 1998, Hamburg, Germany, June 30-July 4, 1998, and at the Annual Meeting of the American Society of Anesthesiologists, Orlando, Florida, October 17-21, 1998.

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BY the use of autoradiographic methods, we recently demonstrated in rats that sevoflurane and isoflurane both induce a decrease in glucose utilization and an increase in blood flow of the brain compared with conscious controls.¹ These effects were less pronounced for sevoflurane than for isoflurane. The local analysis revealed further that local cerebral blood flow (LCBF) is mainly adjusted to the local metabolic demands at 1 minimum alveolar concentration (MAC) and to a lesser extent at 2 MAC for isoflurane and sevoflurane.¹ Because desflurane has the lowest blood gas solubility coefficient among all volatile anesthetics available,² promoting a fast recovery from anesthesia, in addition to its stability in soda lime,³ desflurane appears to be well-suited for an-

esthesia. Therefore, in the current investigation, our observations were extended to include desflurane.

Materials and Methods

The current study was performed using a protocol identical to our previous investigation.¹ In brief, after approval by the institutional animal care committee, 60 male Sprague-Dawley rats (Charles River Deutschland, Sulzfeld, Germany), weighing 333 ± 40 g (mean \pm SD) were randomly assigned to the following five experimental groups: group 1: conscious controls anesthetized with halothane-nitrous oxide-oxygen for femoral vessel cannulation only; groups 2 and 3: rats anesthetized by isoflurane; groups 4 and 5: rats anesthetized by desflurane (Suprane; Pharmacia & Upjohn, Erlangen, Germany; Devapor; Dräger, Lübeck, Germany) each at 1 (groups 2 and 4) or 2 MAC (groups 3 and 5) in air-oxygen (fraction of inspired oxygen $[F_{iO_2}]$, 0.3). After femoral vessel cannulation, tracheostomy, induction of artificial ventilation, muscle relaxation using pancuronium, to preserve comparability to previous autoradiographic investigations,⁴⁻⁶ the rats in groups 2-5 were allowed to equilibrate for 60 min at the desired MAC level. In the conscious group (group 1), rats recovered from halothane-nitrous oxide-oxygen anesthesia for 3 h. Then 4-iodo-*N*-methyl- $[^{14}C]$ antipyrine was infused over 1 min for the measurement of LCBF in 40 brain regions of interest in half of the animals of each group. The other half of the animals was treated identically, with the exception that 2- $[^{14}C]$ -deoxy-D-glucose was infused over 20 s for the measurement of local cerebral glucose utilization (LCGU), and the equilibration time at the desired MAC level was reduced from 60 to 45 min to obtain approximately median points of the tracer measurements for LCGU and LCBF.^{7,8} At the end of the measurement periods (LCGU, 45 min; LCBF, 1 min), the animals were killed and the brains were removed, frozen, sectioned into 20- μ m sections at -20°C , and autoradiographed, along with precalibrated $[^{14}C]$ methyl methacrylate standards. LCGU or LCBF were calculated from the local concentrations of $[^{14}C]$ and the time course of plasma $[^{14}C]$ deoxyglucose and glucose concentrations⁸ (lumped constant, 0.483) or the the blood iodo $[^{14}C]$ antipyrine⁹ (blood partition coefficient of iodoantipyrine, 0.9).¹⁰ Mean CBF and mean CGU were determined from the average of the area-weighted means of coronal sections taken from the whole brain and spaced at distances of 200 μ m. Data were analyzed by

analysis of variance and *t* tests (significance assumed for $P < 0.05$) with Bonferroni correction. The overall relation between LCGU and LCBF in the evaluated regions was assessed by the least-squares fit of the data.

Results

Similar to isoflurane, desflurane induced a significant decrease in mean arterial blood pressure. Other physiologic parameters were comparable between the five experimental groups. Compared with the conscious state, mean CGU was significantly reduced by both anesthetics to 48% of the control value ($55 \pm 5 \mu\text{mol} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$) at 1 MAC desflurane ($27 \pm 4 \mu\text{mol} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$), to 56% of the control value at 1 MAC isoflurane ($31 \pm 7 \mu\text{mol} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$), to 38% of the control value at 2 MAC desflurane ($21 \pm 2 \mu\text{mol} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$), and to 40% of the control value at 2 MAC isoflurane ($22 \pm 4 \mu\text{mol} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$). No significant difference was observed between both anesthetics at identical MAC levels. The considerable decrease in glucose utilization observed on a global level was also evident from the local values. LCGU was decreased in the majority of brain structures investigated during isoflurane anesthesia and in all brain structures investigated during desflurane anesthesia. Compared to the conscious state ($88 \pm 6 \text{ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$) mean CBF was increased by 40% during desflurane anesthesia at 1 MAC ($124 \pm 27 \text{ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$) and by 43% during isoflurane anesthesia ($126 \pm 18 \text{ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$). At 2 MAC mean CBF was increased by 68% during desflurane anesthesia ($148 \pm 14 \text{ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$) and by 70% during isoflurane anesthesia ($150 \pm 15 \text{ml} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$). No significant difference in mean CBF was observed between both anesthetics at identical MAC levels. The increase in CBF observed for the whole brain was also evident from the local values. LCBF was increased in all of the 40 brain structures investigated during anesthesia, except for in the auditory cortex in which LCBF was reduced at an increasing anesthetic depth. At 1 MAC isoflurane and desflurane, a close coupling between blood flow and metabolism could be seen for all 40 brain structures analyzed (fig. 1). At 2 MAC, coupling was mainly preserved. The lower correlation coefficients observed at 2 MAC compared with 1 MAC were because of the finding that, in some brain regions, metabolism was not or was only slightly decreased during either isoflurane or desflurane anesthesia.

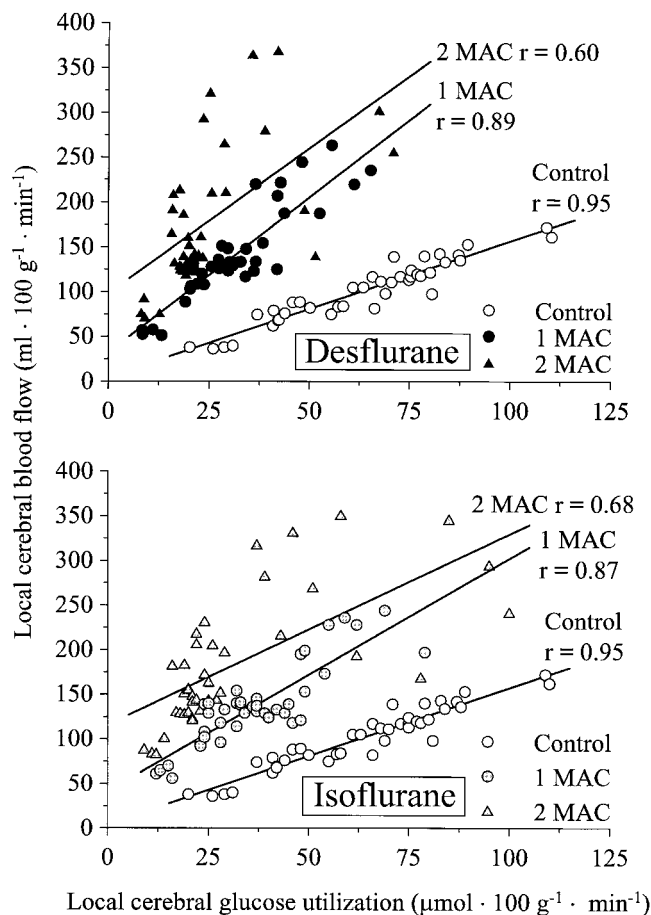


Fig. 1. Coupling of local cerebral blood flow (LCBF) to local cerebral glucose utilization (LCGU) in 40 brain structures during 1 and 2 MAC isoflurane anesthesia (bottom) and desflurane anesthesia (top) compared with conscious control rats ($n = 6$ for each LCGU value and each LCBF value at all MAC levels). The regression lines were calculated according to $y = ax + b$, where y is LCBF and x is LCGU. Control: $y = 1.5x + 4.9$; isoflurane 1 MAC: $y = 2.6x + 42.2$; isoflurane 2 MAC: $y = 2.1x + 116$; desflurane 1 MAC: $y = 3.5x + 32.1$; desflurane 2 MAC: $y = 3.2x + 98.4$.

Discussion

This study extends our previous work regarding isoflurane and sevoflurane anesthesia.¹ The decrease of mean CGU observed in rats during 1 MAC and 2 MAC desflurane anesthesia (52 to 62%) was similar to that obtained during sevoflurane (34 to 59%)¹ anesthesia. Lutz *et al.*¹¹ measured a smaller decrease in the metabolic rate of oxygen (26%) in dogs, when the end-tidal concentration of desflurane was increased from 0.5 MAC to 2.0 MAC.¹¹ This difference may be explained by the light anesthesia of the control group in the study of Lutz *et al.*,¹¹ decreasing baseline values of metabolic rate of oxygen, whereas

conscious animals were used as controls in the current investigation. LCGU during desflurane anesthesia showed a more uniform decrease in the current study compared with the metabolic effects observed during sevoflurane anesthesia¹ and other anesthetics analyzed previously.^{6,12-22} Whereas the increase of mean CBF during sevoflurane anesthesia was significantly lower at 2 MAC than the increase during isoflurane anesthesia,¹ no differences in mean CBF could be found between isoflurane and desflurane at both MAC levels investigated. Few other studies have described CBF during desflurane anesthesia.^{11,23-25} An increase in the end-tidal concentration of desflurane from 0.5 MAC to 2 MAC induced an increase in CBF by 43% when mean arterial pressure was maintained by infusion of phenylephrine in dogs.¹¹ The smaller change in CBF compared with the finding in rats (+68%)¹ may again be explained by the slight anesthesia used for control measurements by Lutz *et al.*¹¹ In humans, no difference in CBF could be observed between desflurane and isoflurane anesthesia at an end-tidal concentration of 1.25 MAC and a partial pressure of arterial carbon dioxide (P_{aCO_2}) of 35 mmHg.²⁵ This finding in humans is in accordance with that of the current study in rats. Local analysis of blood flow in the current study showed that LCBF was moderately reduced in the auditory cortex during desflurane and isoflurane anesthesia, in contrast to all other brain structures in which LCBF was increased. The decrease of LCBF in auditory cortex was paralleled by the largest reduction of LCGU measured among all cortical structures (desflurane, -80%; isoflurane, -82% at 2 MAC). If blood flow is coupled to metabolism on a local level, the reduction of LCBF could therefore be explained by the decreased metabolic demand of the tissue that is not completely compensated for by vasodilative effects of the volatile anesthetics in the auditory cortex. The current investigation shows that the local coupling between LCGU and LCBF found during conscious control conditions²⁶ is preserved during anesthesia induced by 1 MAC desflurane or isoflurane, although the relation is reset to higher levels of blood flow. During 2 MAC desflurane and isoflurane anesthesia, some brain structures in which no or only slight decreases in the metabolic rate could be measured during anesthesia seemed to deviate from this pattern. These results confirm observations from previous coupling studies of Hansen *et al.*⁷ for 1 MAC halothane and isoflurane, Maekawa *et al.*⁶ for 1 and 2 MAC isoflurane, and our own findings during sevoflurane anesthesia at 1 and 2 MAC.¹ During 1 MAC isoflurane anesthesia, in all three studies, coupling parameters

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can be found in similar ranges (Maekawa *et al.*⁶: $r = 0.82$; $LCBF = 2.2 \times LCGU + 67$ [calculated from published data⁶]; Hansen *et al.*⁷: $r = 0.78$; $LCBF = 1.9 \times LCGU + 47$; the current investigation: $r = 0.87$; $LCBF = 2.6 \times LCGU + 42$). In contrast, during 2 MAC isoflurane anesthesia, a lower correlation between LCBF and LCGU values is observed (Maekawa *et al.*⁶: $r = 0.45$; $LCBF = 2.6 \times LCGU + 208$; the current investigation: $r = 0.68$; $LCBF = 2.4 \times LCGU + 99$).^{1,6,7} In conclusion, the current investigation shows that desflurane induces a decrease of global glucose use and an increase of global blood flow in the brain that are comparable to those induced by isoflurane. The local analysis reveals a slightly more uniform decrease of LCGU during desflurane than during isoflurane anesthesia. Finally, the correlation (coupling) between LCGU and LCBF is reset during desflurane and isoflurane anesthesia, although it is preserved at 1 MAC and to a lesser extent at 2 MAC during desflurane anesthesia.

References

1. 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
2. Eger EI II: Partition coefficients of I-653 in human blood, saline, and olive oil. *Anesth Analg* 1987; 66:971-3
3. Eger EI III: Stability of I-653 in soda lime. *Anesth Analg* 1987; 66:983-5
4. Ueki M, Mies G, Hossmann KA: Effect of alpha-chloralose, halothane, pentobarbital and nitrous oxide anesthesia on metabolic coupling in somatosensory cortex of rat. *Acta Anaesthesiol Scand* 1992; 36:318-22
5. Samra SK, Turk P, Arens JF: Effect of hypocapnia on local cerebral glucose utilization in rats. *ANESTHESIOLOGY* 1989; 70:523-6
6. 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
7. 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
8. Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M: The [¹⁴C]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
9. Sakurada O, Kennedy C, Jehle J, Brown JD, Carbin GL, Sokoloff L: Measurement of local cerebral blood flow with iodo [¹⁴C] antipyrine. *Am J Physiol* 1978; 234:H59-66
10. Schröck H, Kuschinsky W: Cerebral blood flow, glucose use, and CSF ionic regulation in potassium-depleted rats. *Am J Physiol* 1988; 254:H250-7
11. Lutz LJ, Milde JH, Milde LN: The cerebral functional, metabolic, and hemodynamic effects of desflurane in dogs. *ANESTHESIOLOGY* 1990; 73:125-31
12. McQueen JK, Martin MJ, Harmar AJ: Local changes in cerebral 2-deoxyglucose uptake during alphaxalone anaesthesia with special reference to the habenulo-interpeduncular system. *Brain Res* 1984; 300:19-26
13. Herkenham M: Anesthetics and the habenulo-interpeduncular system: selective sparing of metabolic activity. *Brain Res* 1981; 210:461-6
14. Hodes JE, Soncrant TT, Larson DM, Carlson SG, Rapoport SI: Selective changes in local cerebral glucose utilization induced by phenobarbital in the rat. *ANESTHESIOLOGY* 1985; 63:633-9
15. Crosby G, Crane AM, Sokoloff L: Local changes in cerebral glucose utilization during ketamine anesthesia. *ANESTHESIOLOGY* 1982; 56:437-43
16. Duffy TE, Cavazzuti M, Cruz NF, Sokoloff L: Local cerebral glucose metabolism in newborn dogs: Effects of hypoxia and halothane anesthesia. *Ann Neurol* 1982; 11:233-46
17. Savaki HE, Desban M, Glowinski J, Besson MJ: Local cerebral glucose consumption in the rat: I. Effects of halothane anesthesia. *J Comp Neurol* 1983; 213:36-45
18. Cole DJ, Shapiro HM: Different 1.2 MAC combinations of nitrous oxide-enflurane cause unique cerebral and spinal cord metabolic responses in the rat. *ANESTHESIOLOGY* 1989; 70:787-92
19. Nakakimura K, Sakabe T, Funatsu N, Maekawa T, Takeshita H: Metabolic activation of intercortical and corticothalamic pathways during enflurane anesthesia in rats. *ANESTHESIOLOGY* 1988; 68:777-82
20. Ori C, Dam M, Pizzolato G, Battistin L, Giron G: Effects of isoflurane anesthesia on local cerebral glucose utilization in the rat. *ANESTHESIOLOGY* 1986; 65:152-6
21. Shapiro HM, Greenberg JH, Reivich M, Ashmead G, Sokoloff L: Local cerebral glucose uptake in awake and halothane-anesthetized primates. *ANESTHESIOLOGY* 1978; 48:97-103
22. Myers RR, Shapiro HM: Local cerebral metabolism during enflurane anesthesia: Identification of epileptogenic foci. *Electroencephalogr. Clin Neurophysiol* 1979; 47:153-62
23. Lutz LJ, Milde JH, Milde LN: The response of the canine cerebral circulation to hyperventilation during anesthesia with desflurane. *ANESTHESIOLOGY* 1991; 74:504-7
24. Milde LN, Milde JH: The cerebral and systemic hemodynamic and metabolic effects of desflurane-induced hypotension in dogs. *ANESTHESIOLOGY* 1991; 74:513-8
25. Ornstein E, Young WL, Fleischer LH, Ostapkovich N: Desflurane and isoflurane have similar effects on cerebral blood flow in patients with intracranial mass lesions. *ANESTHESIOLOGY* 1993; 79:498-502
26. Kuschinsky W: Coupling of function, metabolism, and blood flow in the brain. *News Physiol Sci* 1987; 2:217-220