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Effects of Pentobarbital and Isoflurane on Regional Cerebral Oxygen Extraction and Consumption with Middle Cerebral Artery Occlusion in Rats

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Background: **When compared with barbiturates, isoflurane may lack protective effects during focal cerebral ischemia. The reason for this difference is not clear. In this study, regional cerebral blood flow (rCBF), arterial and venous O_2 saturation, and O_2 extraction were compared in the ischemic cortex and in the nonischemic brain regions of rats anesthetized with isoflurane or pentobarbital using a microspectrophotometric technique that directly measures the O_2 saturation of blood in the small arteries and veins.**

Methods: **Twenty-eight rats were anesthetized with 1.4% isoflurane or 50 mg/kg pentobarbital. One hour after a middle cerebral artery (MCA) occlusion, rCBF was measured in the ischemic cortex and in the nonischemic brain regions using ^{14}C-iodoantipyrine in one-half of each group of animals. Regional arterial and venous O_2 saturation were determined using microspectrophotometry in the other one-half of each group.**

Results: **The rCBF of the ischemic cortex (IC) and the nonischemic contralateral cortex (CC) of the isoflurane group were significantly higher than those of the pentobarbital group. The venous O_2 saturation was significantly less, and the O_2 extraction was significantly higher, in the IC than in the nonischemic regions in both groups of animals (pentobarbital group, IC 10.5 ± 1.1 ml $O_2 \cdot 100$ ml blood^{-1}, CC 6.3 ± 0.7; isoflurane group, IC 10.8 ± 0.6, CC 5.9 ± 0.2). There was no significant difference between the two groups.**

Conclusions: **Because the rCBF was less and the O_2 extraction was similar, O_2 consumption in the focal ischemic area of the brain during pentobarbital anesthesia must have been less than that during isoflurane anesthesia. (Key words: Anesthetics, intravenous: pentobarbital. Anesthetics, volatile: isoflurane. Brain: cerebral ischemia.)**

IT has been suggested that barbiturates have protective effects against focal cerebral ischemia.[1-4] Reduction of the cerebral metabolic rate of oxygen by barbiturates is considered to be the main mechanism of brain protection. Using a microspectrophotometric technique, we have shown that regional arterial and venous O_2 saturation and O_2 extraction were not different in the brain regions between conscious and pentobarbital anesthetized animals.[5] However, regional cerebral blood flow (rCBF) and regional O_2 consumption in each brain region were less in animals anesthetized with pentobarbital than in awake animals. Isoflurane may have some protective properties during a global ischemia or hypoxia of the brain.[6] When compared with barbiturates, however, isoflurane may lack the protective effect during focal ischemia,[3,4] and produces higher rCBF in the ischemic cortex than that produced by barbiturates.[4]

In this investigation, we compared the effect of barbiturate and isoflurane on cerebral energy metabolism by measuring rCBF and arterial and venous O_2 saturation in the ischemic cortex. In most studies of regional energy metabolism in the brain, glucose utilization has been used. However, measuring the accumulation of 2-deoxyglucose as an index of brain metabolism may not be appropriate during a stroke, because of the limitation of this method in the low-flow state.[7,8] Our microspectrophotometric technique can overcome the restriction that limits the usefulness of glucose utilization.[9-12] With this technique, arterial and venous oxygen saturation can be measured directly in the ischemic area of the brain. Combined with measurements of the rCBF, the cerebral regional oxygen consumption can be estimated from the Fick principle. The purpose of the current investigation was to compare the effects of pentobarbital and isoflurane on venous O_2 saturation,

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O_2 extraction, and O_2 consumption in the focal ischemic area of the rat brain. Ischemia was induced by middle cerebral artery (MCA) occlusion, and the microspectrophotometric technique was used to directly measure arterial and venous oxygen saturation in the ischemic area.

Materials and Methods

This study was approved by our institutional animal care and use committee. Data are reported here from 28 adult male Long-Evans rats weighing 330–450 g. They were divided into two groups of 14 each: a pentobarbital group and an isoflurane group. Seven animals in each group were used for the blood-flow study, and the seven others in each group were used to determine the arterial and venous O_2 saturation.

For the pentobarbital group, animals were anesthetized with sodium pentobarbital (50 mg/kg intraperitoneally). A femoral artery and vein were catheterized and a craniotomy was performed. The arterial catheter was used to monitor the heart rate and the blood pressure, and to anaerobically obtain arterial blood samples for the analysis of blood gases and *p*H. The venous catheter was used to administer ^{14}C-iodoantipyrine for blood-flow measurement. Additional pentobarbital (15 mg/kg intraperitoneally) was administered 40–50 min after the initial dose.

For the isoflurane group, rats were anesthetized with 2% Isoflurane in a mixture of air and oxygen (FI_{O_2} 0.25–0.3). A tracheostomy was performed for mechanical ventilation. A femoral artery and vein were catheterized and a craniotomy was performed. Isoflurane concentration was decreased to 1 MAC (1.4%) 10 min before MCA ligation.[13]

Surgical procedures for MCA exposure and occlusion were modified from those of Tamura *et al.*[14] An incision was made near the superior and posterior margins of the temporalis muscle. The infratemporal fossa was exposed. A hole was drilled at the junction between the medial wall and the roof of the infratemporal fossa, and the artery was occluded as close to the base of the skull as possible.

Body temperature was monitored and maintained at 37° C with a servocontrolled rectal thermistor probe and a heating lamp. Arterial blood pressure was continuously measured using a Statham P23AA transducer (Gould Instruments, Cleveland, OH) coupled to the arterial catheter and recorded on a Beckman R-411 recorder (Fullerton, CA). Normal saline (2–3 ml · $kg^{-1} \cdot h^{-1}$) was infused to the rats of the isoflurane group to account for the evaporative loss from the airway. Arterial blood was withdrawn anaerobically and analyzed for P_{O_2}, P_{CO_2}, and *p*H on a blood gas analyzer (BMS model 3, Radiometer America, Westlake, OH), and the hemoglobin concentration was determined spectrophotometrically before determining cerebral blood flow (CBF) and O_2 saturation.

Measurement of the Cerebral Blood Flow

One hour after MCA occlusion, ^{14}C-iodoantipyrine (Amersham, Arlington Heights, IL) was infused into the venous catheter by means of an infusion pump (Sage Instruments, Cambridge, MA). At the time of entry of the isotope into the venous circulation, the arterial catheter was cut to a length of 15–20 mm to minimize smearing in the sampling catheter. Timed blood samples were withdrawn from the arterial catheter and collected approximately every 3 s in capillary tubes. These samples were collected over a period of 60 s, at which time the rat was decapitated at the moment the last sample was obtained. The head was quickly frozen in liquid nitrogen for later analysis. While frozen, the head was cut in the midsagittal plane, and the following regions were dissected and weighed: ischemic parietal cortex (area which was discolored by MCA occlusion), contralateral parietal cortex, contralateral basal ganglia, and pons. Blood and tissue samples were then placed in a tissue solubilizer (Soluene, Packard, Downers Grove, IL) and, 24 h later, they were put in a counting fluid (Dimiscint, National Diagnostic, Manville, NJ) and agitated. These samples were counted on a Beckman LS-230 liquid scintillation counter. Quench curves were prepared using carbon tetrachloride, while the isotope counts were adjusted for color and quench correction.

Regional blood flow was calculated using a computer program based on the following equation:

$$Ci(T) = \lambda K \int_0^T C_A e^{-K(T-t)} dt,$$

where Ci(T) = the tissue concentration of ^{14}C-iodoantipyrine at the time of decapitation; λ = the tissue: blood partition coefficient; C_A = the arterial concentration of the tracer; and t = time. K is defined as K = mF/W; where m is the constant related to diffusion; and F/W equals the blood flow per unit mass of tissue. The λ value of 0.8 calculated by Sakurada *et al.* was used.[15]

Measurement of Oxygen Saturation

Regional arterial and venous O_2 saturation were determined 1 h after MCA occlusion. The head was frozen in liquid nitrogen as soon as the rat was decapitated. The frozen brains, stored in liquid nitrogen until analyzed, were cut into wafers with a band saw located in a room held at −20° C. The following four regions were isolated and examined: ischemic cortex, contralateral cortex, contralateral basal ganglia, and pons. Samples were prepared for microspectrophotometric analysis, as previously described.[9-12] Briefly, 20 μm of thick frozen tissue sections were cut on a cold rotary microtome in a −25° C cold box that was flushed with nitrogen. Each section was then transferred to a precooled glass slide, covered with degassed silicone oil and a cover slip, and rapidly transferred to the nitrogen-flushed cold stage of the microspectrophotometer. Small arteries and veins, identified by the presence or absence of the muscular media (20–100 μm diameter) were examined, and the O_2 saturation of blood contained within the vessels was determined with measurements of optical densities at 523, 560, and 568 nm. The three-wavelength method corrects for light scattering in the frozen blood. Microspectrophotometric measurements were obtained from a total of eight to ten veins and five arteries per region. The volume of tissue examined in each region was approximately 0.5 cm^3. Vessels located exclusively in the transverse section were studied so that the path of light traversed only the blood.

Determination of Oxygen Extraction

Oxygen extraction was determined by the formula

$$(SaO_2 - Sv_{O_2}) \times Hb \times 1.36,$$

where Sa_{O_2} and Sv_{O_2} = average regional arterial and venous O_2 saturation, respectively, which were measured quantitatively; Hb = systemic hemoglobin concentration of each individual rat; and 1.36 = the maximum oxygen binding capacity of the hemoglobin.

Statistical Analysis

A factorial analysis of variance was applied for the various measurements performed to determine the difference between brain regions and groups. Multiple comparisons were made using Duncan's *post hoc* procedure. The chi-square test and coefficient of variation (CV) were used to compare changes in heterogeneity. The CV was calculated as SD/mean × 100. All values are expressed as mean ± SD. A P value < 0.05 was considered to be statistically significant.

Table 1. Hemodynamic and Blood Gas Parameters for Rats 1 h after Unilateral MCA Occlusion

	Pentobarbital (n = 14)	Isoflurane (n = 14)
Systolic blood pressure (mmHg)	115 ± 18	118 ± 11
Diastolic blood pressure (mmHg)	89 ± 9	84 ± 10
Mean blood pressure (mmHg)	98 ± 10	95 ± 9
Heart rate (beats/min)	334 ± 27	322 ± 37
Pa_{O_2} (mmHg)	90 ± 10	93 ± 10
Pa_{CO_2} (mmHg)	40 ± 4	39 ± 3
*p*H	7.39 ± 0.06	7.36 ± 0.03
Hemoglobin (g/100 ml)	14.2 ± 1.6	14.3 ± 0.4

Values are mean ± SD.

MCA = middle cerebral artery.

Results

Hemodynamic and blood gas parameters for the two groups are presented in table 1. Both groups of animals had similar hemoglobin, blood pressure, temperature, and blood gases. There was no statistical difference between the pentobarbital and isoflurane groups in the hemodynamic and blood gas parameters.

rCBF in the various examined regions of the two groups is presented in figure 1. In all of the brain regions we studied, rCBF was greater in the isoflurane group than in the pentobarbital group. The rCBF of the ischemic cortex was significantly decreased to 53% of that of the contralateral cortex in the pentobarbital group. In the isoflurane group, rCBF of the ischemic cortex was also significantly decreased to 46% of that of the contralateral cortex. The rCBF of the ischemic cortex of the isoflurane group was 51.7 ± 11.3 $ml \cdot min^{-1} \cdot 100\ g^{-1}$, and was significantly greater than that of the pentobarbital group (34.4 ± 14.6 $ml \cdot min^{-1} \cdot 100\ g^{-1}$).

Regional cerebral arterial O_2 saturation was not significantly different between the two groups, nor was it so among the brain regions we studied, including the ischemic cortex (table 2).

Average regional cerebral venous O_2 saturation (Sv_{O_2}) was significantly decreased in the ischemic cortex of the pentobarbital group (41.9 ± 2.3%) when compared with that of the contralateral cortex (62.8 ± 2.7%) (table 2). In the isoflurane group, the average

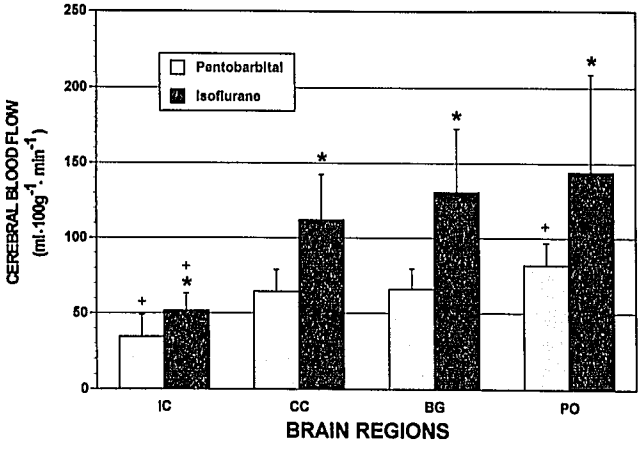

Fig. 1. Regional cerebral blood flow in the pentobarbital and isoflurane groups 1 h after middle cerebral artery occlusion. IC = ischemic cortex; CC = contralateral cortex; BG = basal ganglia; PO = pons; +significantly different from the corresponding contralateral cortex; *significantly different from the pentobarbital group.

Table 2. Arterial and Venous Oxygen Saturation and Cerebral Oxygen Extraction 1 h after MCA Occlusion

	Arterial O_2 Saturation (%)	Venous O_2 Saturation (%)	O_2 Extraction (ml O_2/100 ml blood)
Ischemic cortex			
Pentobarbital	94.8 ± 1.9	41.9 ± 2.3*	10.5 ± 1.1*
Isoflurane	96.2 ± 1.6	40.7 ± 1.1*	10.8 ± 0.6*
Contralateral cortex			
Pentobarbital	94.7 ± 1.5	62.8 ± 2.7	6.3 ± 0.7
Isoflurane	95.2 ± 7.5	65.0 ± 0.8	5.9 ± 0.2
Basal ganglia			
Pentobarbital	94.9 ± 1.5	63.6 ± 2.0	6.0 ± 0.3
Isoflurane	94.3 ± 1.1	64.6 ± 2.6	5.8 ± 0.7
Pons			
Pentobarbital	94.7 ± 2.3	62.2 ± 3.3	6.5 ± 0.9
Isoflurane	94.9 ± 1.4	65.4 ± 2.1	5.8 ± 0.5

Values are mean ± SD.

MCA = middle cerebral artery.

* Significantly different from the corresponding contralateral cortex.

venous O_2 saturation of the ischemic cortex (40.7 ± 1.1%) was also much lower than that of the contralateral cortex (65.0 ± 0.8%). Figure 2 shows that the distribution of the Sv_{O_2} of small veins was shifted to the left after MCA occlusion in both groups of animals. There was no significant difference in the Sv_{O_2} of the ischemic cortex between the pentobarbital and the isoflurane group. The Sv_{O_2} of the ischemic cortex of both groups followed a normal distribution curve. In the ischemic cortex, the Sv_{O_2} in 62 small cerebral veins of the pentobarbital group showed a dispersion with a coefficient of variation (CV = SD/mean × 100) of 13.1. In the ischemic cortex of the isoflurane group, Sv_{O_2} in 56 small veins varied with a CV of 9.2. However, there was no statistical difference in heterogeneity of Sv_{O_2} between the two groups. The CV of the ischemic cortex was not different from that of the nonischemic cortex in both groups of animals. The CV of the two groups was similar in the contralateral cortex (pentobarbital 9.8 and isoflurane 7.3). There was no significant difference in the Sv_{O_2} of various nonischemic brain regions between these two groups and among various brain regions. The Sv_{O_2} of the nonischemic brain regions of both groups followed a normal distribution, as well.

Oxygen extraction was significantly increased, from 6.3 ± 0.7 ml O_2 · 100 ml blood^{-1} in the contralateral cortex to 10.5 ± 1.1 ml O_2 · 100 ml blood^{-1} in the ischemic cortex of the pentobarbital group (table 2). For the isoflurane group, the O_2 extraction was also significantly greater in the ischemic cortex (10.8 ± 0.6 ml O_2 · 100 ml blood^{-1}) than in the contralateral cortex (5.9 ± 0.2). There were no significant differences in O_2 extraction among the various nonischemic regions or between the pentobarbital and the isoflurane groups in any brain region.

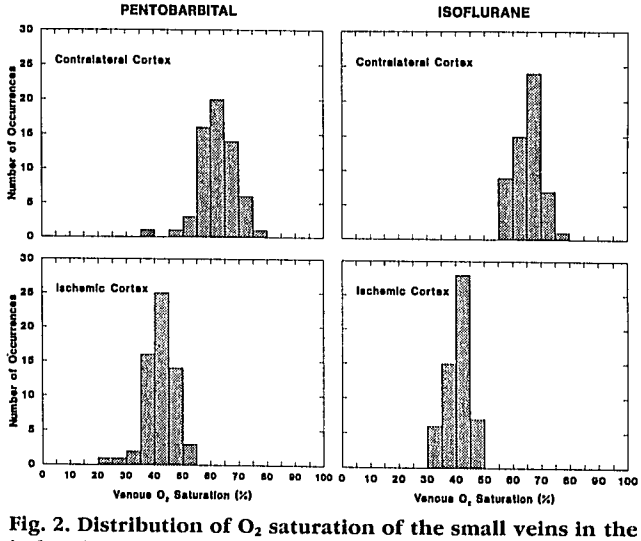

Fig. 2. Distribution of O_2 saturation of the small veins in the ischemic cortex and the contralateral cortex in the pentobarbital and the isoflurane group. The distribution of O_2 saturation is shifted to the left after MCA occlusion in both groups of animals.

Discussion

From our data, regional cerebral O_2 consumption can be estimated using the Fick principle as a product of the mean of rCBF and the mean of O_2 extraction, as shown in figure 3. In the ischemic cortex of the pentobarbital group, the O_2 consumption was 88% of that in the corresponding contralateral cortex, and 36% less than that of the ischemic cortex in the isoflurane group. In each nonischemic brain region, the O_2 consumption of the pentobarbital group was 35–45% less than that of each corresponding region of the isoflurane group.

The major finding of this investigation was that, with MCA occlusion, CBF was decreased and oxygen extraction was increased, and this helped to maintain the local oxygen consumption. Because the rCBF was lower and the O_2 extraction was similar, O_2 consumption in the focal ischemic area of the brain during pentobarbital anesthesia must have been lower than that during isoflurane anesthesia.

In our study, we administered 1 MAC of isoflurane and 50 mg/kg pentobarbital. With this pentobarbital dose, our previous study demonstrated that O_2 consumption decreased by about 50% from that of conscious animals.[5] In other studies, 1 MAC of isoflurane decreased the local glucose utilization in most of the cortical area by 45–55% from that of conscious animals.[16,17] We did not expect that the absolute value of regional cerebral O_2 consumption at these doses of anesthetics would, necessarily, be the same. We chose this dose of anesthetic because higher doses, which cause EEG burst suppression, significantly jeopardize vital signs. Nevertheless, in the ischemic area, rCBF was usually reduced to about 50% when compared with the nonischemic area.[11,12] At this level of rCBF, EEG usually becomes slow, and animals would not require a high dose of pentobarbital or isoflurane to suppress electric activity of the brain.[18,19]

The rCBF of the nonischemic areas in rats anesthetized with isoflurane in our study was very similar to that of other studies.[16,20] However, the percentage of the decrease in rCBF in the ischemic cortex was lower than those of the studies that measured rCBF using an autoradiographic technique.[4,21] We used the "tissue chunk" method. For ischemic brain tissue, we sampled the cortical tissue that was discolored by MCA occlusion. It is possible that our samples of the ischemic cortex could have been mixed with mildly ischemic or nonischemic brain tissue. In our study, rCBF in each brain region, including the ischemic cortex of the isoflurane group, was 1.5–2 times that of the pentobarbital group. A similar pattern of high rCBF was observed in the study of Warner *et al.*, who used an autoradiographic technique.[4] They observed that the rCBF of the isoflurane-treated animals was about three times that of the methohexital-treated animals in each brain region, including the ischemic area, at the dose of anesthetics that produced EEG burst suppression.

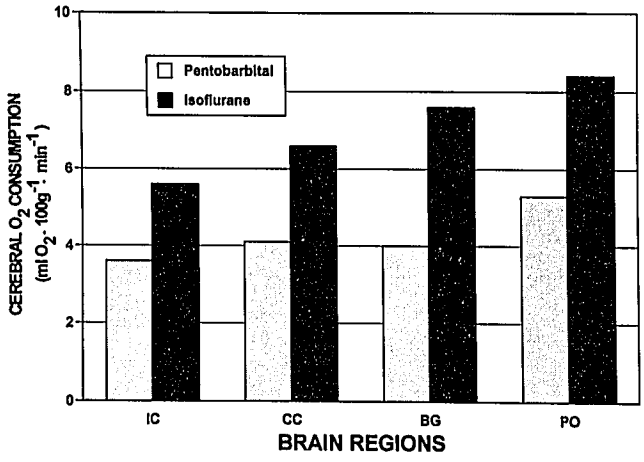

Fig. 3. Regional cerebral oxygen consumption in the pentobarbital and isoflurane groups 1 h after middle cerebral artery occlusion. Oxygen consumption of the ischemic cortex (IC) of the pentobarbital group was 88% of that of the corresponding contralateral cortex (CC) and 36% less than that of the ischemic cortex of the isoflurane group. Other regions studied were the basal ganglia (BG) and pons (PO).

Results of the measurement of venous O_2 saturation, rCBF, O_2 extraction, and O_2 consumption in the ischemic cortex and in the nonischemic brain regions of the pentobarbital group in our study are similar to those of previous studies.[11,12]

Our method of determining cerebral O_2 extraction with microspectrophotometry depends on the ability to freeze the tissue quickly to arrest the blood flow. Our previous study showed that it takes about 3 s for the brain to freeze after plunging it into liquid nitrogen. If the brain is frozen within 15–30 s, no significant change in venous oxygen saturation occurs. Only when the freezing time exceeds 45 s does venous oxygen saturation decrease significantly.[11] This finding is consistent with previous validation studies performed on other organs.[9,22]

In our study, instead of brain temperature, core temperature was monitored and was maintained at 37° C. Because previous reports on rCBF and O_2 consumption in the ischemic cortex were similar to those of this

study,[4,12] the effect of difference in the site of temperature monitoring should be minimal.

Ideally, blood flow and oxygen saturation should be performed in the same animals. However, because the size of the ischemic tissue produced by MCA ligation in a rat was not large enough to perform both measurements, we used different animals for these analyses. Consequently, the oxygen extraction and flow measurements in a region may not correspond exactly. Furthermore, sources of drainage of the 20–100-μm venules examined may be from an area somewhat distant from that of the flow measurement. Therefore, one must study a reasonable number of venules to determine the average oxygen consumption of an ischemic region.

Glucose utilization is used in most studies on energy metabolism. However, it is difficult to measure this in the ischemic brain.[23,24] During the low-flow state, changes may occur in the lumped constant that make the calculation of glucose utilization questionable.[7,8] Also, anaerobic metabolism of glucose may change the relationship between glucose utilization and cerebral oxygen metabolism. Our microspectrophotometric technique eliminates these restrictions of the glucose utilization technique. The 2-deoxyglucose method averages the metabolic rate of small areas of the brain for 45 min. In comparison, the microspectrophotometric technique measures the O_2 saturation of venous blood at a certain moment. Previously, using microspectrophotometry, we showed that there was no change in oxygen consumption after MCA ligation in the central region and the region surrounding the infarct.[11] In contrast, the glucose-uptake technique showed that the utilization of glucose increased in the border zone and decreased in the central zone.[24,25]

In both groups of animals, venous O_2 saturation showed some degree of heterogeneity (pentobarbital group: CV, IC 13.1, CC 9.8; isoflurane group: CV, IC 9.2, CC 7.3). The degree of heterogeneity, which is expressed as coefficient of variation, was similar among all the brain regions, including the ischemic cortex, and was also similar between the two anesthetic groups. This heterogeneity has been previously reported.[5,11,12] It may indicate that cerebral microregional blood flow is not precisely matched to the metabolic rate at every moment. Another plausible source of the observed variation could be the opening and closure of various capillary beds in the brain, although this concept of recruitment of vasculature in the brain is a controversial one.

In our study, compensation for a decrease in CBF was achieved by increased O_2 extraction, and regional O_2 consumption was maintained in the ischemic cortex in both groups of animals. This implies that either there was little cell death at this time, or those living cells were consuming more oxygen.

Our study also showed that O_2 extraction was similar in both the pentobarbital and the isoflurane groups. However, calculated O_2 consumption was higher in each of the brain regions of the isoflurane group than in the pentobarbital group at the dose and concentration we used. In the ischemic cortex, O_2 consumption of the pentobarbital group was 36% lower than that of the isoflurane group. There may be an association between other reports of increased cell survival and our data showing lower oxygen consumption in the ischemic region during pentobarbital anesthesia than during isoflurane anesthesia. The ischemic region may be better able to survive a decreased blood flow or oxygen supply if the oxygen consumption is reduced. It is not clear why pentobarbital affected the metabolism of oxygen and not oxygen extraction in the ischemic area. This may be related to the degree of flow restriction, or the lack of full balance between flow and metabolism in ischemia. Some cells may be dead and, therefore, causing no changes in oxygen balance. Other characteristics of barbiturates, such as a reduction in calcium influx, an inhibition of free radicals, an ability to block sodium channels, and an action on excitatory and inhibitory amino acid neurotransmitters, should be considered as the mechanism of brain protection during cerebral ischemia.[26–31]

In conclusion, we demonstrated that, in the ischemic area of the brain, compensation for a decrease of rCBF was achieved by increased O_2 extraction, and regional O_2 consumption was maintained in both groups of animals. Because the rCBF was less, and the O_2 extraction was similar, in the ischemic cortex during pentobarbital anesthesia when compared with isoflurane anesthesia, the O_2 consumption in the focal ischemic area of the brain must have been less during pentobarbital anesthesia than during isoflurane anesthesia. This lower O_2 consumption in the ischemic cortex during pentobarbital anesthesia than during isoflurane anesthesia could contribute to the mechanism of protection by barbiturates in focal cerebral ischemia.

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