Responses of EEG, cerebral oxygen consumption and blood flow to peripheral nerve stimulation during thiopentone anaesthesia in the dog

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The effects of sciatic nerve stimulation on the electroencephalogram (EEG), cerebral metabolic rate for oxygen (CMRO₂) and cerebral blood flow (CBF) were investigated during thiopentone anaesthesia in dogs. Anaesthetic levels at 15, 35, 65, 95 and 125 minutes after the start of thiopentone infusion (23 mg·kg⁻¹·hr⁻¹) were designated levels I, II, III, IV and V, respectively. The effects of stimulation for 5 min were tested at each level. At level I (plasma thiopentone concentration; 15 ± 2 µg·ml⁻¹), the EEG was activated with stimulation and CMRO₂ and CBF increased by a maximum of 16 and 15 per cent, respectively. The increase in CMRO₂ and CBF was significant for five and four minutes, respectively, though the increase became less with time. At level II (27 ± 3 µg·ml⁻¹), the CMRO₂ and CBF increased at one minute by eight and nine per cent, the increase being accompanied by transient EEG activation. At the three

deepest levels III, IV and V (37 ± 6, 42 ± 6, 49 ± 6 µg·ml⁻¹), the EEG, CMRO₂ and CBF remained unchanged with stimulation. The results suggest the existence of the tight coupling between the EEG, CMRO₂ and CBF and of a threshold level of thiopentone to block the response to peripheral stimulation during thiopentone anaesthesia.

Key words

ANAESTHETICS, INTRAVENOUS: thiopentone.

BRAIN: electroencephalogram; stimulation. BRAIN: blood flow, metabolism.

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A dose of barbiturate sufficient to produce an anaesthetic state is known to cause electroencephalographic (EEG) slowing which is accompanied by the reduction of the cerebral metabolic rate for oxygen (CMRO₂) and cerebral blood flow (CBF).¹ This suggests that a close relationship exists between function, metabolism and blood flow during barbiturate anaesthesia, as observed during wakefulness² and in chronic brain disease.³ However, such a relationship does not necessarily exist under all anaesthetic circumstances, since it is known that volatile anaesthetics cause EEG slowing and a decrease in CMRO₂, but an increase in CBF. These studies on CMRO₂ and CBF have been concerned only with the effects of anaesthetics without stimulation. In our laboratory, Kuramoto *et al.*⁴ studied modification of EEG, CMRO₂ and CBF responses to stimulation by halothane, methoxyflurane, nitrous oxide and morphine. The data suggested that the coupling of the EEG and CMRO₂ was maintained but the coupling of CMRO₂ and CBF varied with anaesthetics and anaesthetic levels. In the

FIGURE 1 Changes of mean CMRO₂, CBF and absolute plasma concentrations of thiopentone. Vertical bars indicate $\pm$ SEM. The times, 15, 35, 65, 95 and 125 min after the start of infusion correspond to anaesthetic levels I, II, III, IV and V, respectively.

present study, this approach was extended to thiopentone which is known to be a potent cerebral vasoconstrictor. We found tight coupling between EEG, CMRO₂ and CBF during stimulation.

Methods

Ten unpremedicated mongrel dogs weighing 10 to 21 kg were anaesthetized with 1 to 1.5 per cent halothane, in 40 per cent oxygen and nitrogen. Succinylcholine, 2 mg·kg⁻¹, was given intramuscularly to facilitate tracheal intubation and thereafter, was given at the rate of 1 mg·kg⁻¹·hr⁻¹. Ventilation was controlled by a Harvard animal respirator to maintain PaO₂ at 25 ± 0.3 kPa (mean $\pm$ SEM) and PaCO₂ at 5.1 ± 0.1 kPa. Oesophageal

temperature and haemoglobin levels were maintained at $37 \pm 0.1^\circ\text{C}$ and 12 ± 0.2 g·dL⁻¹, respectively.

Both femoral arteries were cannulated for blood sampling and pressure measurement, and both femoral veins were cannulated for the infusion of blood, lactated Ringer's solution and drugs. Both sciatic nerves were carefully exposed and cut at the thigh level. Their proximal ends were then gently placed on bipolar silver-silver chloride electrodes, separated by 1 cm. Sciatic nerve temperature was maintained by circulating warmed liquid paraffin around the exposed area. The surgical preparation used for the measurement of hemispheric CBF was as originally described by Michenfelder *et al.*⁵ and

subsequently modified by Oshita *et al.*⁶ After the animal was heparinized, using an initial dose of $3 \text{ mg} \cdot \text{kg}^{-1}$, then $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$, the sagittal sinus was cannulated. The drained blood was returned to the left external jugular vein through the draining cannula.

An electromagnetic flowmeter probe (lumen diameter 3 mm) was incorporated 1 cm away from the draining portion of the sinus. To ensure exact measurements, the flowmeter (Nihon Kodan MF-46) incorporated a nonocclusive zero and a 3-sec time constant. In addition, the flowmeter was frequently calibrated by direct timed measurements of the sagittal sinus blood flow. After postmortem injection of vinyl acetate into the sinus and subsequent dissection, the weight of the brain drained by the cannula was found to average 41 ± 1 per cent of the total brain, and the absence of extracerebral venous connections to the sagittal sinus was confirmed. This percentage is used to correct units of flow from $\text{mL} \cdot \text{min}^{-1}$ to $\text{mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. The oxygen content of the arterial and sagittal sinus blood was calculated from measurements of oxyhemoglobin (IL 282 CO-oxymer) and oxygen tension (ABL-2 electrode). Blood pH and PCO_2 values were measured with appropriate electrodes. The CMRO_2 was calculated as the product of CBF and the difference in oxygen content of the arterial and sagittal sinus blood. Cerebral vascular resistance (CVR) was calculated as the ratio of mean arterial pressure (MAP) to CBF. The EEG was continuously recorded using parietal bipolar silver-silver chloride electrodes.

After completion of the surgical preparation, the inspired halothane concentration was decreased to 0.2 per cent in 40 per cent oxygen and nitrogen, and these concentrations of background gases were maintained throughout the study. At least one hour was allowed to elapse before the start of the measurements. Lidocaine, $5 \text{ mg} \cdot \text{kg}^{-1}$ (0.5 per cent solution), was injected into the skin and muscle of the head and at the areas where the cannulae were placed. Additional lidocaine (half of the initial dose) was given hourly.

The mean values of CMRO_2 and CBF were obtained from five to seven consecutive determinations before the start of thiopentone infusion. Thereafter, thiopentone was infused intravenously at a constant rate of $23 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ and the anaesthetic levels at 15, 35, 65, 95 and 125 minutes

were designated level I, II, III, IV and V. At each level of anaesthesia, a control measurement was obtained one minute before stimulation. Following the control measurement, bilateral sciatic nerve stimulation was done by application of supramaximum rectangular stimuli (6 volts, 0.1 msec, 100 Hz) for 5 min. During the stimulation, CMRO_2 and CBF were measured at 1-min intervals, along with the continuous monitoring of EEG. A decrease in amplitude or an increase in frequency, or both were considered a manifestation of EEG activation. Plasma thiopentone concentrations were measured at each level by gas chromatography (Shimadzu GC-4).

Statistical differences were tested by one-way analysis of variance for repeated measurement with the least significant difference test for multiple comparisons. $P < 0.05$ was considered significant.

Results

Before thiopentone infusion, the EEG mainly consisted of 13–20 Hz waves and the mean CMRO_2 and CBF were 6.0 ± 0.2 and $59 \pm 3 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, respectively. Per cent changes of CMRO_2 and CBF during thiopentone infusion as compared to the values before thiopentone are illustrated in Figure 1 in association with plasma concentrations of thiopentone. Plasma thiopentone concentration was 15 ± 2 , 27 ± 3 , 37 ± 6 , 42 ± 6 and $49 \pm 6 \mu\text{g} \cdot \text{mL}^{-1}$ (mean $\pm$ SEM) at levels I, II, III, IV and V, respectively. The values represent the mean of the two samples obtained before and at the end of the 5-minute stimulation period. At level I, the CMRO_2 and CBF decreased to 83 and 84 per cent of the value before thiopentone, respectively. These changes were accompanied by EEG slowing, which consisted of 2 to 8 Hz superimposed on 8 to 13 Hz waves. Thereafter, the mean CMRO_2 and CBF decreased progressively in association with further slowing of the EEG (levels II and III) and with a decrease in amplitude (level IV). At level V, while the EEG showed burst suppression, the mean CMRO_2 and CBF decreased to 57 and 58 per cent of the value before thiopentone, respectively.

The effects of sciatic nerve stimulation on cerebral metabolism and circulation are summarized in the Table. Representative EEG patterns are shown in Figure 2. With the stimulation at level I, the EEG was highly activated and the mean CMRO_2 and CBF increased by a maximum of 16 and 15 per cent at one minute, and remained elevated for five- and

FIGURE 2 Representative EEGs before (control) and, at 1 and 5 min after the start of stimulation at each anaesthetic level. EEG activation was observed at level I (1, 5 min) and II (1 min) but not at the three deepest levels.

four-minute stimulation periods, respectively, with a tendency for a decrease in response with time. At level II, the EEG initially showed an activated pattern, and the $CMRO_2$ and CBF increased significantly by eight and nine per cent, respectively, at the first minute. Thereafter, the changes substantially decreased with time. At levels III, IV and V, the EEG, $CMRO_2$ and CBF were unaffected by the stimulation. Regression analysis between the $CMRO_2$ and CBF at the five different anaesthetic levels revealed a significant correlation ($r = 0.98$) between metabolism and flow as shown in Figure 3.

Discussion

The present study has demonstrated the existence of a coupling between the EEG, $CMRO_2$ and CBF responses to sciatic nerve stimulation during thiopentone anaesthesia at all anaesthetic levels tested. The tight coupling between metabolism and flow

was distinct when pooled $CMRO_2$ and CBF values at the different levels were tested for regression analysis. The magnitude of the increase in $CMRO_2$ and CBF with stimulation at level I and II could be biased by baseline shifts of $CMRO_2$ and CBF, particularly during the latter half of the stimulation period, since $CMRO_2$ and CBF were decreased by the continuous thiopentone infusion. However, this underestimation would be at most 0.5 per cent for each one minute period for $CMRO_2$ and CBF change at level I and II, and does not affect the conclusions. The decrease in response of $CMRO_2$ and CBF to stimulation with time, being marked in level II, may indicate the deepening level of anaesthesia with thiopentone and/or the accommodation of the sciatic nerve itself or the somatosensory pathway to the stimulation, as also observed by Kuramoto *et al.*⁴ The authors had anticipated EEG activation and increases in $CMRO_2$ and CBF even

TABLE Effects of sciatic nerve stimulation on cerebral metabolism and circulation

Level	Time after stimulation (min)	CMRO ₂ (ml·100 g ⁻¹ ·min ⁻¹)	CBF (ml·100 g ⁻¹ ·min ⁻¹)	MAP (mmHg)	CVR (mmHg·ml·100 g ⁻¹ ·min ⁻¹)
I	Control	4.95 ± 0.16	49.1 ± 2.5	94 ± 4	1.96 ± 0.14
	1	5.76 ± 0.23*	56.3 ± 3.0*	96 ± 7	1.74 ± 0.15*
	2	5.46 ± 0.17*	55.1 ± 2.9*	94 ± 5	1.77 ± 0.14*
	3	5.57 ± 0.20*	54.2 ± 3.0*	92 ± 4	1.76 ± 0.14*
	4	5.42 ± 0.19*	52.6 ± 2.9*	91 ± 4	1.79 ± 0.15*
	5	5.50 ± 0.21*	51.9 ± 3.1	91 ± 4	1.82 ± 0.15*
II	Control	4.52 ± 0.18	43.8 ± 2.9	92 ± 4	2.17 ± 0.14
	1	4.86 ± 0.24*	47.6 ± 3.3*	85 ± 5*	1.87 ± 0.16*
	2	4.84 ± 0.24	46.3 ± 3.3	87 ± 4*	1.96 ± 0.15*
	3	4.72 ± 0.23	45.4 ± 3.3	86 ± 4*	1.98 ± 0.16*
	4	4.71 ± 0.24	44.4 ± 3.2	85 ± 4*	2.00 ± 0.16*
	5	4.73 ± 0.24	44.1 ± 3.3	85 ± 4*	2.01 ± 0.16*
III	Control	4.09 ± 0.21	38.0 ± 2.9	87 ± 4	2.41 ± 0.21
	1	4.13 ± 0.20	38.5 ± 2.9	74 ± 5*	2.04 ± 0.22*
	2	4.13 ± 0.21	38.0 ± 3.0	79 ± 5*	2.19 ± 0.23*
	3	4.17 ± 0.21	37.8 ± 3.0	78 ± 5*	2.18 ± 0.23*
	4	4.13 ± 0.20	37.5 ± 3.0	77 ± 6*	2.17 ± 0.22*
	5	4.12 ± 0.17	37.4 ± 2.9	77 ± 5*	2.18 ± 0.23*
IV	Control	3.72 ± 0.14	35.9 ± 3.2	88 ± 4	2.61 ± 0.24
	1	3.76 ± 0.15	36.3 ± 3.4	73 ± 4*	2.21 ± 0.24*
	2	3.72 ± 0.16	35.7 ± 3.4	77 ± 4*	2.33 ± 0.23*
	3	3.72 ± 0.15	35.7 ± 3.3	78 ± 4*	2.33 ± 0.23*
	4	3.73 ± 0.14	35.7 ± 3.3	77 ± 4*	2.32 ± 0.23*
	5	3.74 ± 0.14	35.2 ± 3.3	76 ± 4*	2.32 ± 0.22*
V	Control	3.43 ± 0.12	34.2 ± 3.1	84 ± 4	2.63 ± 0.25
	1	3.48 ± 0.13	33.5 ± 3.0	76 ± 4*	2.41 ± 0.23*
	2	3.49 ± 0.12	33.7 ± 3.1	77 ± 4*	2.44 ± 0.25*
	3	3.52 ± 0.12	33.8 ± 3.1	76 ± 4*	2.42 ± 0.25*
	4	3.50 ± 0.12	33.8 ± 3.0	77 ± 5*	2.45 ± 0.26*
	5	3.50 ± 0.12	33.8 ± 3.1	78 ± 5*	2.46 ± 0.25*

Values are Mean ± SEM.

*Significantly different from control ($p < 0.05$).

during the deeper levels of thiopentone anaesthesia (levels III, IV and V), since barbiturates are known to be weak in blocking noxious stimuli. However, cerebral metabolic and circulatory responses to the sciatic nerve stimulation became undetectable with increasing dose of thiopentone. Therefore, the threshold of the plasma concentration of thiopentone at which EEG, metabolic and circulatory responses to stimuli would be blocked seems to be somewhere between 27 $\mu\text{g}\cdot\text{ml}^{-1}$ (level II) and 37 $\mu\text{g}\cdot\text{ml}^{-1}$ (level III). This plasma level of thiopentone is slightly lower than the reported values in humans for loss of corneal reflex and trapezius

muscle response (39–42 $\mu\text{g}\cdot\text{ml}^{-1}$) which are reported to be well correlated with the response to surgical stimulation.⁷

Meyer *et al.*⁸ reported that stimulation of the brain-stem reticular formation produced EEG activation and increases in CMRO₂ and CBF of eight and ten per cent, respectively, during pentobarbitone and ether anaesthesia in the monkey, but with femoral nerve stimulation, there was no significant change in CMRO₂ and CBF. The latter was only tested in two monkeys. The inexact nature of their reported anaesthetic conditions make detailed comparison difficult. Langfitt and Kassell⁹ reported that

FIGURE 3 Linear regression analysis between the CMRO₂ and CBF at the five different anaesthetic levels.

the stimulation of the lower brain-stem invariably altered the EEG pattern and produced an increase in CBF without a change in blood pressure in five cord-sectioned monkeys anaesthetized with pentobarbitone. They concluded that the most likely explanation for the cerebral vasodilatation was a neurogenic mechanism, because of the very short time between stimulation and response. However, they did not measure CMRO₂, making examination of the relationship between metabolism and blood flow impossible.

In rabbits anaesthetized with chloralose and urethane, Gregory *et al.*¹⁰ reported that increased CBF due to sciatic nerve stimulation paralleled an increase in local metabolism, and that the increase in CBF was independent of the change in MAP, since sciatic nerve stimulation resulted in a decrease in MAP. Increase of glucose consumption in the discrete area in the spinal cord and cerebral cortex with peripheral nerve stimulation during pentobar-

bitone or nitrous oxide anaesthesia has been also reported.¹¹ In this study, however, the effects of different doses of pentobarbitone was not tested. The present study shows the existence of threshold level of thiopentone to block the response to stimulation. The parallel change in CMRO₂ and CBF with stimulation observed in the present study suggests that cerebral vasodilatation occurs in response to demand for oxygen during increased neuronal activities.

Kuramoto *et al.*⁴ studied modification of the relationship between cerebral metabolism, blood flow and EEG by sciatic nerve stimulation during different types of anaesthesia. During halothane anaesthesia, sciatic nerve stimulation produced a striking increase in CBF even at the stage where no EEG and CMRO₂ response were seen. In contrast with morphine, which is a mild cerebral vasoconstrictor, there was coupling between CMRO₂ and CBF during stimulation. They suggested that

coupling between CMRO₂ and CBF may be related to the cerebral vascular effects of individual anaesthetics, and appears to be dependent on whether a specific drug dilates or constricts cerebral vessels. This was supported by the present results, since thiopentone is known to be a potent cerebral vasoconstrictor.

In the present study, MAP decreased with stimulation at levels II, III, IV and V. Such a decrease in MAP was also observed with sciatic nerve stimulation during deep halothane or methoxyflurane anaesthesia.⁴ However, during light halothane, methoxyflurane and morphine anaesthesia, MAP increased with peripheral stimulation.⁴ This suggests that individual effects of anaesthetics on vasomotor response to peripheral stimulation may be variable.

It is well known that in neurosurgical anaesthesia an increase in CBF may be harmful, especially for the patient who already had an increased intracranial pressure.¹² In this respect, thiopentone, if the adequate dose is given, does prevent a striking increase in CBF with peripheral stimulation as seen in halothane, and, hence, seems to be a suitable agent for the patient with increased intracranial pressure.

In summary, during thiopentone anaesthesia there was a tight coupling between the EEG, CMRO₂ and CBF, either with or without sciatic nerve stimulation. At the EEG stage of marked slow waves or burst suppression, there were no cerebral metabolic and circulatory responses to supramaximum stimulation of the sciatic nerve in the dog.

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Résumé

Les effets de la stimulation du nerf sciatique sur l'électroencéphalogramme (EEG), consommation d'oxygène par le cerveau ($CMRO_2$) ainsi que le flot cérébral (CBF) ont été investigués lors de l'anesthésie au thiopentone chez les chiens. Les niveaux d'anesthésie à 15, 35, 65, 95 et 125 minutes après le début de la perfusion du thiopentone ($23 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$) ont été définis comme étant les niveaux I, II, III, IV et V. Les effets d'une stimulation de cinq minutes ont été étudiés à chaque niveau. Au niveau I (concentration plasmatique de thiopentone; $15 \pm 2 \text{ } \mu\text{g} \cdot \text{ml}^{-1}$), l'EEG a été activé par la stimulation et la $CMRO_2$ et le CBF ont augmenté de 16 et 15 pour cent respectivement. L'augmentation de la $CMRO_2$ et du CBF a été significative pour cinq et quatre minutes respectivement même si l'augmentation a diminué avec le temps. Au niveau II ($27 \pm 3 \text{ } \mu\text{g} \cdot \text{ml}^{-1}$), le $CMRO_2$ et le CBF ont augmenté à une minute de huit et neuf pour cent, l'augmentation étant accompagnée par une activation transitoire de l'EEG. Aux trois niveaux les plus profonds III, IV et V (37 ± 6 , 42 ± 6 , $49 \pm 6 \text{ } \mu\text{g} \cdot \text{ml}^{-1}$), l'EEG, la $CMRO_2$ et le CBF sont restés inchangés avec la stimulation. Les résultats suggèrent une liaison étroite entre l'EEG, la $CMRO_2$ et le CBF ainsi que les niveaux du thiopentone qui bloqueraient la réponse à une stimulation périphérique.