Modification of the Relationship between the Electroencephalogram, Cerebral Metabolism and Blood Flow by Stimulation During Halothane Anesthesia in the Dog

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(Received May 23, 1977)

SUMMARY

The effects of sciatic nerve stimulation on the electroencephalogram (EEG), cerebral circulation and metabolism were investigated at four different anesthetic levels of halothane. With 0.2, 0.5 and 0.9 per cent halothane, the cerebral metabolic rate for oxygen ($CMRo_2$) increased to a maximum of 116, 119 and 120 per cent of control, respectively, and was accompanied by desynchronization of EEG. At the same time, the cerebral blood flow (CBF) increased, but the responses varied with different levels of anesthesia. With 1.4 per cent halothane, the $CMRo_2$ and the EEG remained unchanged from control but the CBF increased to a maximum of 135 per cent of control and remained above 120 per cent of control throughout the stimulation. These results suggest that the coupling of $CMRo_2$ and EEG was maintained at all concentrations but that the coupling of $CMRo_2$ and CBF was variable with different levels of anesthesia.

INTRODUCTION

Great interest has been focused on the interrelationship between cerebral function, metabolism and blood flow[1]. The coupling of regional or global cerebral blood flow (CBF) to function in conscious men[2] and in chronic brain disease[3] has been repeatedly stressed in the literature and it is believed by some[4] that changes in regional CBF reflect cerebral metabolic changes and hence the functional state of a particular region of the brain. In contrast, recent studies have revealed the differential effects of anesthetics on the electroencephalogram (EEG)[5,6], CBF and cerebral metabolism[7,8], thus emphasizing the complexity of anesthesic mechanisms in the central nervous system[9]. The EEG monitoring com-

bined with well validated CBF measurement originally described by Michenfelder and his associates[10], allowed us to study the effect of sciatic nerve stimulation on EEG, $CMRo_2$ and CBF, in the dog anesthetized with halothane, and it was found that there was a clear coupling between $CMRo_2$ and EEG, whereas the interrelationship between $CMRo_2$ and CBF was variable with different anesthetic levels.

MATERIALS AND METHODS

Eight unpremedicated mongrel dogs weighing 12 to 25 kg were anesthetized with halothane (1 to 1.5%, inspired) in oxygen and nitrogen. Succinylcholine was given to facilitate tracheal intubation and thereafter gallamine was administered at 50 mg per hour to maintain muscle paralysis. Ventilation was controlled with a Harvard pump during the measurements to maintain a constant $Paco_2$ of 36 ± 0.5 (SE) torr. Pao_2 was maintained at 188 ± 8 torr by the adjustment of ventilation and FIO_2. An epidural thermistor was placed to monitor the brain temperature which was maintained at 37 ± 0.5 °C with the aid of an electric heating pad. Hemoglobin levels were maintained at 14 ± 0.2 g/dl by appropriate blood replacement. Mean arterial pressure during the control measurement was maintained above 80 torr in all dogs. In order to maintain this pressure level in dogs subjected to 1.4 per cent halothane anesthesia, phenylephrine, which is reported to have no effect on cerebral circulation and metabolism[11], was administered.

Both femoral arteries were cannulated for blood sampling and pressure measurements, and both femoral veins were cannulated for the infusion of blood and lactated Ringer's solution. Both sciatic nerves were carefully exposed and were cut at the thigh level. Their proximal ends were then gently placed on bipolar silver-silver chloride electrodes which were separated 1 cm from each other. Sciatic nerve temperature was maintained by circulating warmed liquid paraffin around the exposed area. Supramaximal rectangular stimuli (6 volts, 0.1 msec, 100 Hz) were applied for 5 minutes through the electrodes to initiate desynchronization of the EEG.

The surgical preparation that we used for the measurement of CBF was originally described by Michenfelder et al.[10] After the animal was heparinized by an initial dose of 3 mg/kg (1 mg/kg/hr, subsequently), cannulation of the saggital sinus was performed. The drained blood was returned to the left external jugular or mandibular vein through the draining cannula. Around this draining cannula a suitably sized electromagnetic flowmeter probe with a lumen diameter of 3 mm was placed. To

insure exact measurements, the electromagnetic flowmeter (Nihon Kohden, MF-46) incorporated a nonocclusive zero and a 3.0-sec time constant. In addition, the electromagnetic flowmeter was frequently calibrated by direct timed measurement of the sagittal sinus blood flow. The percentage of the total brain weight drained from the saggital sinus was determined by injecting vinyl acetate at the completion of each experiment and was used to convert units of flow from ml/min to ml/100g/min. Oxygen content of the arterial or sagittal sinus blood was calculated from measurements of oxyhemoglobin (IL 182 Co-oximeter) and oxygen tension (IL 313 electrode). pH and Pco_2 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 bilateral silver-silver chloride electrodes.

After completing the surgical preparations, inspired halothane was introduced at a level of 0.2 per cent and thereafter at least 1 hr was elapsed before the start of experiment. Control measurements were ob ta-ined during each level of anesthesia over a 15 to 20-minute period and the mean values were calculated from 5 to 8 consecutive determinations of CBF and $CMRo_2$. Following control measurements, the stimulation of both sciatic nerves was applied as described above for 5 minutes. During the stimulation, arterial and sagittal sinus blood were sampled at 0.5, 1, 1.5, 2, 3, 4 and 5 minutes. Halothane concentration was then increased to 0.5, 0.9 and 1.4 per cent in a stepwise manner, and in each case equilibrium was reached within 20 to 30 minutes after the change of inspired concentration. The concentration of end-tidal halothane was monitored by a gaschromatograph.

At the end of the experiment it was confirmed that autoregulation of the CBF from 50 to 150 torr (using induced hemorrhage and phenylephrine infusion) was intact and that the CBF increased appropriately in response to the addition of 5 to 15 per cent CO_2.

No evidence of extracerebral contamination of sagittal sinus blood or other cerebral vascular abnormalities was found at autopsy.

All the data were subjected to analysis of variance. Statistical differences of $P<0.05$ were considered to be significant.

RESULTS

The effects of sciatic nerve stimulation on cerebral circulation and metabolism during 0.22 ± 0.01, 0.49 ± 0.02, 0.90 ± 0.01 and 1.40 ± 0.04

per cent halothane anesthesia are summarized in tables 1, 2, 3 and 4, respectively. Representative EEG patterns with corresponding $CMRo_2$ values are shown in Fig. 1. The time course of the per cent changes in CBF and $CMRo_2$ are shown in Fig. 2.

0.2 per cent halothane: The EEG was desynchronized by electric stimulation and thereafter the frequency of fast wave activities tended to decrease with time. The $CMRo_2$ was increased by 16 per cent 1 minute after the start of stimulation and later gradually decreased to the control level. The CBF increased to a maximum of 150 per cent at 0.5 minutes after the beginning of stimulation and then declined gradually toward the control level.

0.5 per cent halothane: The control EEG at this anesthetic level had a higher voltage slower frequency than that at the 0.2 per cent

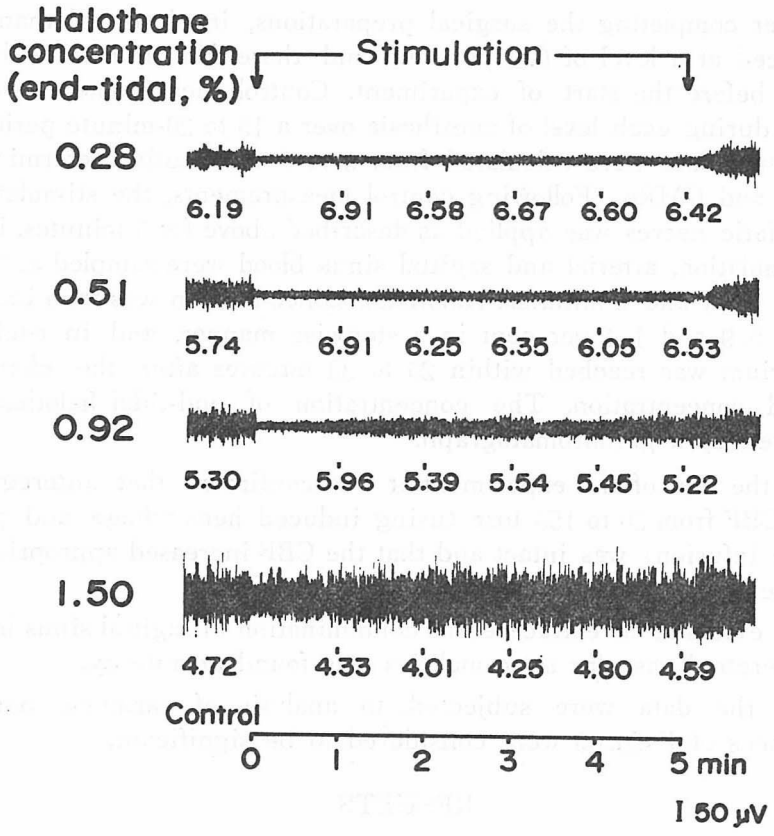

Fig 1. Representative EEG and $CMRo_2$. The numbers under each EEG tracing indicate the value of $CMRo_2$ at that time.

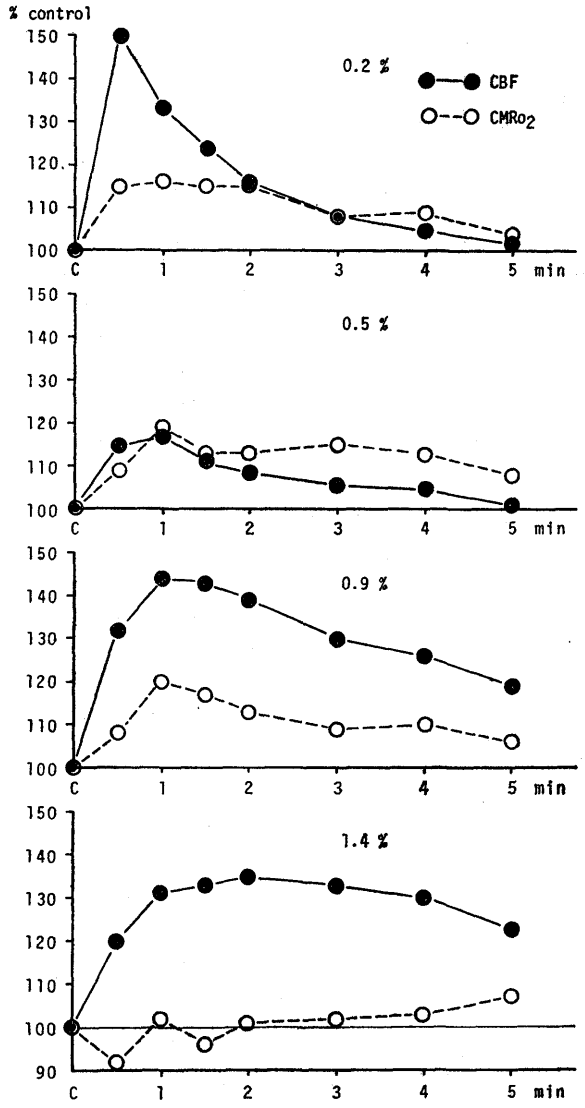

Fig. 2. Time course of CBF and $CMRo_2$ expressed as per cent of control. Closed circle indicates the CBF and open circle indicates the $CMRo_2$.

level, but became highly desynchronized by the stimulation, and remained desynchronized throughout the stimulation. The $CMRo_2$ showed a 19 per cent increase at 1 minute and this increase was maintained above 13 per cent until the 4th minute. By contrast, the CBF was only slightly increased during the lst minute and soon returned to the control level.

Table 1. Effects of sciatic nerve stimulation on cerebral circulation and metabolism during 0.2 per cent halothane anesthesia

Time after stimulation (min)	MAP (torr)		CBF (ml/100g/min)		CVR (torr/ml/1000g/min)		$CMRo_2$ (ml/100g/min)		$Psso_2$** (torr)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Contro	115	4	61	4	1.95	0.14	5.80	0.40	31	2
0.5	175*	8	91*	10	2.03	0.17	6.64*	0.47	38*	2
1	146*	4	82*	9	1.88	0.12	6.74*	0.44	36*	2
1.5	139*	5	75*	8	1.92	0.11	6.67*	0.49	35*	2
2	135*	6	70	7	2.01	0.13	6.64*	0.53	34*	2
3	129	6	65	6	2.05	0.14	6.28	0.44	32	2
4	125	6	64	5	2.03	0.14	6.31	0.46	32	2
5	118	6	62	5	1.98	0.14	6.00	0.47	33	2

* Significantly different from control ($P<0.05$).
** $Psso_2$: Oxygen tension of sagittal sinus blood.

Table 2. Effects of sciatic nerve stimulation on cerebral circulation and metabolism during 0.5 per cent halothane anesthesia

Time after stimulation (min)	MAP (torr)		CBF (ml/100g/min)		CVR (torr/ml/100g/min)		$CMRo_2$ (ml/100g/min)		$Psso_2$ (torr)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Control	104	5	64	6	1.69	0.12	5.37	0.31	34	1
0.5	112	6	74*	5	1.55	0.11	5.87*	0.39	35	2
1	106	3	75*	5	1.44*	0.09	6.37*	0.32	35	1
1.5	102	3	71*	6	1.48*	0.10	6.06*	0.38	34	2
2	101	4	70	6	1.50*	0.11	6.07*	0.31	33	1
3	93	3	68	6	1.41*	0.08	6.17*	0.40	33	1
4	92	4	67	6	1.42*	0.08	0.05*	0.37	33	1
5	93	4	65	6	1.49*	0.08	5.82	0.37	33	1

* Significantly different from control ($P<0.05$)

Thus, the degree of initial CBF increase observed during 0.2 per cent halothane anesthesia was markedly inhibited by 0.5 per cent halothane, whereas the increase in $CMRo_2$ was similar as was the desynchronization of the EEG.

0.9 per cent halothane: The EEG showed a moderately desynchronized pattern initially due to stimulation, but was less than that of the two previously described levels of anesthesia. Toward the end of stimulation the EEG was almost identical to the control pattern. The $CMRo_2$

Table 3. Effects of sciatic nerve stimulation on cerebral circulation and metabolism during 0.9 per cent halothane anesthesia

Time after stimulation (min)	MAP (torr)		CBF (ml/100g/min)		CVR (torr/ml/100g/min)		$CMRo_2$ (ml/100g/min)		$Psso_2$ (torr)	
	Mean	SE	Mean	SE	Meap	SE	Mean	SE	Mean	SE
Control	91	4	67	8	1.46	0.13	5.03	0.15	37	2
0.5	94	5	88*	10	1.13*	0.10	5.43	0.37	42*	3
1	93	5	96*	12	1.06*	0.11	6.02*	0.32	43*	2
1.5	92	5	96*	13	1.06*	0.12	5.88*	0.35	44*	3
2	92	5	93*	11	1.07*	0.12	5.66	0.31	43*	2
3	92	4	87*	8	1.11*	0.10	5.50	0.37	43*	2
4	92	4	84*	7	1.13*	0.10	5.55	0.32	43*	2
5	90	4	79*	6	1.17*	0.09	5.35	0.35	41*	2

* Significantly different from control ($P<0.05$)

Table 4. Effects of sciatic nerve stimulation on cerebral circulation and metabolism during 1.4 per cent halothane anesthesia

Time after stimulation (min)	MAP (torr)		CBF (ml/100g/min)		CVR (torr/ml/100g/min)		$CMRo_2$ (ml/100g/min)		$Psso_2$ (torr)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Control	92	3	91	8	1.07	0.11	4.94	0.24	49	3
0.5	91	6	110*	7	0.85*	0.08	4.55	0.38	54*	3
1	92	7	119*	9	0.80*	0.07	5.06	0.38	55*	3
1.5	91	6	121*	10	0.78*	0.07	4.72	0.40	57*	3
2	90	6	123*	10	0.76*	0.07	5.01	0.38	55*	3
3	89	6	121*	10	0.76*	0.07	5.02	0.37	55*	3
4	90	7	118*	9	0.79*	0.07	5.09	0.38	54*	2
5	88	6	112*	8	0.82*	0.08	5.29	0.37	53*	2

* Significantly different from control ($P<0.05$)

showed a significant increase only at 1 and 1.5 minutes and in general $CMRo_2$ changes paralleled EEG changes. However, the mean CBF increased significantly throughout most of the stimulation and showed a slight decrease only toward the end of stimulation. After stimulation the CBF gradually returned to the control level over the next 5 minutes.

1.4 per cent halothane: The EEG was unchanged by the stimulation except for the first 5 to 10 seconds, after which it quickly returned to the control pattern. The $CMRo_2$ also remained unaltered. By contrast the CBF increased to a maximum value of 134 per cent of control at 2 minutes

and remained above 120 per cent of control throughout the stimulation. After the cessation of stimulation the CBF gradually returned to the control level over a period of 5 to 10 minutes.

DISCUSSION

The present study indicates the presence of coupling between the EEG (as a reflection of function) and $CMRo_2$ (as a reflection of metabolism) during halothane anesthesia. EEG desynchronization was consistently accompanied by an increase in $CMRo_2$ during 0.2 to 0.9 per cent halothane. Furthermore, the individual time course of the changes in the $CMRo_2$ was closely related to that of the EEG pattern. At 1.4 per cent halothane, neither EEG desynchronization nor an increase in $CMRo_2$ was observed. Thus, at all anesthetic levels there was a tight coupling between cerebral function and metabolism. Meyer et al[12] reported no significant change in $CMRo_2$, EEG and CBF during stimulation of a femoral nerve in two anesthetized monkeys, though they did observe an increase in $CMRo_2$ when the EEG became desynchronized due to stimulation of the reticular formation. Unfortunately, the inexact nature of their reported anesthetic conditions and the differences in methodology make detailed comparison difficult. We are unaware of any other study which examined the relationship between cerebral function, metabolism and blood flow during stimulation.

The results also reconfirm a progressive decrease in the level of $CMRo_2$ with increasing concentrations of halothane. Michenfelder and his associates[13] found a non-linear relationship between $CMRo_2$ and the end-tidal halothane concentration but did relate $CMRo_2$ changes to EEG changes.

If one accepts the assumption that EEG desynchronization by peripheral stimulation is largely dependent upon the activity of the RAS or any of its principle inputs[14], then the present study indicates that metabolic activation below 1 MAC[15] is dependent upon the activity of the RAS. Even if the assumed relationship between the EEG desynchronization and the activity of the RAS is not valid, the coupling of cerebral function and metabolism is still obvious. We had anticipated a decrease in the per cent change in $CMRo_2$ in response to stimulation as anesthesia deepened, but the peak increases in $CMRo_2$ were similar in the three lowest levels of halothane anesthesia from 0.2 to 0.9 per cent and above 1 MAC no increase in the $CMRo_2$ was observed. These results suggest that there may be a threshold effect in terms of evoked metabolic and EEG responses with onset of the anesthetic state. This is compatible

with the non-linear response of $CMRo_2$ previously refered to.

Recent studies have emphasized that regional changes in CBF are related to the functional state of the awake brain. It was shown by Raichle[16] that an increase in regional CBF was accompanied by an increase in regional $CMRo_2$ in awake man. Ingvar and his colleagues[3] have observed a strong correlation between the mean hemispheric $CMRo_2$ and the regional CBF in both awake chronic psychiatric and normal patients. Results of the present study, indicate that during anesthesia there is a poor correlation, at least quantitatively, between CBF and cortical activities as reflected by EEG and $CMRo_2$. During 0.2 per cent halothane anesthesia the time course of the changes in the CBF was almost identical to that of MAP, and the CVR did not show a significant change. This result indicates that the early change in CBF during the administration of 0.2 per cent halothane is mainly dependent upon the change in the MAP, which increased above upper range of autoregulation, rather than $CMRo_2$. On the other hand, the effect of MAP on the CBF at the other three depths of anesthesia should be ignored because the MAP was unaffected, and was even decreased, during these periods of increased CBF. Therefore, the increase in CBF must depend upon vasodilatation. If we accept the theory that cerebral vasodilatation occurs in response to demand for oxygen during increased neuronal activities, then our results at the 0.5 and 0.9 per cent levels of halothane anesthesia may be partially explained by this view. However, this hypothesis does not appear to have any quantitative meaning or applicability because the CBF had a variable relation to the time course of $CMRo_2$ at each level of anesthesia and this variability of response became more exaggerated as anesthesia deepened. Thus, the simplified explanation that cerebral vasodilatation is caused by metabolic demand for oxygen has little credibility as was especially obvious at the 1.4 per cent level of halothane anesthesia.

Langfitt and Kassell[17] reported that brain stem stimulation invariably altered the EEG pattern and produced an increase in CBF without a change in blood pressure in five cord-sectioned monkeys anesthetized with pentobarbital sodium. They concluded that the most likely explanation for the cerebral vasodilatation was the neurogenic mechanism because of the very short time between stimulation and response. In our study, the latent time before the CBF increase was but a few seconds at all levels of anesthesia. Therefore, an alternative explanation of the remarkable change in CBF during 0.5, 0.9 and 1.4 per cent halothane may be the neurogenic mechanism whose reaction was not suppressed by halothane. No direct evidence for a neuronal vasomotor mechanism

can, however, be obtained from the present results.

Cerebral vasodilatation and metabolic depression by halothane are well documented[7,18-20], but most studies are only concerned with the effects of "anesthesia" without surgical stimulation. Therefore, these results may not be directly applicable to the surgical patient. If the peripheral stimulation in the present study is considered analogous to surgical stimulation, then it is obvious that the complete unresponsiveness of blood pressure and EEG to stimulation does not also assure an unresponsive cerebral circulation, even during halothane anesthesia above 1 MAC. The present study strongly suggests that surgical stimulation contributes to a sustained increase in CBF. In neurosurgical anesthesia, it is well known that an increase in CBF may be harmful, especially in the patient who already has an increased intracranial pressure[21]. Therefore, critical attention should be paid to these patients especially at the beginning of surgery.

In conclusion, a close relationship between $CMRo_2$ and the EEG was maintained during halothane anesthesia but the interrelationship between $CMRo_2$ and CBF was variable with different anesthetic levels.

The author greatfully acknowledge the suggestion and encouragement of Prof. H. Takeshita, Department of Anesthesiology.

(This work is a thesis of Graduate School of Medicine, Yamaguchi University)

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