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Cerebral Energy Levels during Trimethaphan-induced Hypotension in the Rat:

Effects of Light versus Deep Halothane Anesthesia

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Hypotension may be expected to produce less perturbation of metabolism in the brain when cerebral metabolic rate is lowered by deep anesthesia. Male Wistar rats having unilateral carotid-artery ligation were exposed to mean arterial pressure (MAP) of 40 torr for 20 min by an intravenous infusion of trimethaphan during anesthesia with halothane, 0.6 or 2 per cent, in oxygen. Cortical tissue metabolite levels on the side of the ligated carotid artery were more abnormal in rats receiving halothane, 0.6 per cent, than in those receiving halothane, 2 per cent. Values at halothane, 0.6 per cent, were adenosine triphosphate (ATP), 1.71 ± 0.05 (±SEM) μmol/g, phosphocreatine (PCr) 1.97 ± 0.07 μmol/g, and lactate 16.5 ± 5.1 μmol/g; corresponding values at halothane, 2 per cent, were ATP 2.27 ± 0.02, PCr 4.02 ± 0.23, and lactate 4.75 ± 0.9 μmol/g. ATP and PCr values were significantly lower ($P < 0.05$) and the lactate value was significantly higher with halothane, 0.6 per cent, than with halothane 2 per cent. Cerebral oxygen consumption decreased 47 per cent in rats anesthetized with halothane, 2 per cent. Preservation of cortical metabolite levels in deeply anesthetized animals suggests a protective effect of cerebral metabolic depression. (Key words: Anesthetics, volatile: halothane. Brain: metabolism, oxygen consumption. Blood pressure: hypotension.)

INDUCED HYPOTENSION continues to be widely employed in surgical anesthesia. Formerly, moderate anesthetic depth produced by volatile agents was commonly used to supplement the effects of ganglion-blocking agents. These volatile agents also decrease cerebral energy consumption, which might afford protection to brain tissue during ischemic substrate depletion. In neuroanesthesia, where cerebrovascular dilation produced by volatile agents may increase intracranial pressure, combination of sodium nitroprusside with nitrous oxide, narcotic, and muscle relaxant drugs has been recommended. With this technique, cerebral metabolic rate remains high; thus, oxygen and substrate depletion secondary to hypotensive ischemia may be poorly tolerated. We have shown that 0.6 and 2 per cent halothane decrease cerebral metabolic rate for oxygen (CMR_{O_2}) in the male Wistar rat by 21 and 47 per cent, respectively.[1] To test the hypothesis that a decrease in cerebral metabolic rate may improve tolerance to hypotensive stress, we have exposed male Wistar rats to a mean arterial pressure of 40 torr for 20 min using trimethaphan infusion combined with halothane, 0.6 or 2 per cent, in oxygen, combined with unilateral carotid-artery ligation.

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Methods

Male Wistar rats (250–350 g) were anesthetized with halothane, 2 to 3 per cent, in oxygen. Through a neck incision, the right carotid artery was separated from the sympathetic trunk and divided between silk ligatures. The wound was closed and the animal permitted to recover from anesthesia. Free access to food and water was allowed until the time of the study.

Two to five days following carotid ligation, each rat was again anesthetized with halothane. Following tracheal intubation with a #7-French catheter using a bivalve nasal speculum, endotracheal anesthesia was maintained with halothane, 0.5 to 0.75 per cent, in nitrous oxide, 70 per cent, in oxygen, with ventilation controlled by a Palmer respirator. Through a midline incision, the tail artery was identified and cannulated with a PE50 catheter, which was connected to a P23DB Statham transducer zeroed at the heart level for arterial pressure recording. A femoral artery and vein were identified through a groin incision and cannulated with a PE50 and a PE60 catheter, respectively, for blood-gas analysis and drug administration. A rectal temperature probe was inserted and body temperature was maintained at 37 C by means of a YSI model A73 with heat-lamp servomechanism. The head was immobilized in a stereotactic head holder, the skull was exposed through a midline scalp incision, and a plastic funnel was sutured into place. At first movement, gallamine triethiodide, 2 mg/kg, was administered via a femoral vein and ventilation was adjusted to maintain Pa_{CO_2} at 39–42 torr. Needle electrodes

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TABLE 1. Mean Arterial Pressure (MAP), Rectal Temperature, Pa_{O_2}, Pa_{CO_2} and pH_a Values before (Control) and during Exposure to Mean Arterial Pressure 40 Torr for 20 Min during Anestheisa with Halothane, 0.6 and 2 Per Cent

	Halothane, 0.6 Per Cent		Halothane, 2 Per Cent	
	Control	Hypotension	Control	Hypotension
MAP (torr)	134 ± 7.8	40 ± 1.4	118 ± 8	40 ± 1.5
Temperature (C)	37.2 ± 0.13	37.3 ± 0.2	37.2 ± 0.2	37.0 ± 0.01
Pa_{O_2} (torr)	237 ± 45	270 ± 57	275 ± 41	314 ± 31
Pa_{CO_2} (torr)	37.4 ± 0.8	41 ± 2.2	37 ± 1	33 ± 2*
pH_a	7.35 ± 0.01	7.22 ± 0.03†	7.40 ± 0.02	7.33 ± 0.04†

All values represent means ± SEM.
* Significantly lower than corresponding value in halothane, 0.6 per cent, group, $P < 0.01$.
† pH_a significantly lower than control, $P < 0.01$.

were inserted for recording the electrocardiogram (EKG) and fronto-occipital electroencephalogram (EEG) on a Gilson polygraph.

Upon completion of the surgical preparation, nitrous oxide was discontinued and the animals, six in each group, were subjected to 30 min of halothane, 0.6 or 2 per cent, in oxygen, for equilibration, following which trimethaphan was infused via a femoral vein using a Harvard infusion pump to maintain mean arterial pressure (MAP) at 39–42 torr for 20 min. Arterial blood-gas and pH values were monitored prior to, during and at the end of the experiment using a model 113 I.L. analyzer. At the end of the 20-min period, trimethaphan infusion was terminated. Immediately after cessation of infusion, liquid nitrogen was poured into the affixed funnel while ventilation was maintained for 5 min, following which the animal was immersed in liquid nitrogen for another 5 min. The frozen brain was then removed *en bloc* and stored in liquid nitrogen for microfluorometric analysis of cerebral cortical adenosine triphosphate (ATP), adenosine diphosphate (ADP), phosphocreatine (PCr), lactate and pyruvate by the method of Lowry and others.[2]

Statistical analysis of the results employed Student's t test for paired data to compare values from right and left hemispheres in the same group, and Student's t test for unpaired data to compare values from respective hemispheres in two different groups. A value of less than 5 per cent was considered significant.

Results

Arterial pressure and body temperature were well maintained within predetermined values in both groups during hypotension (table 1). Pa_{CO_2} was difficult to control and was significantly lower in the group receiving halothane, 2 per cent. However, this extent of hypocapnia has been shown not to have any direct effect on cerebral metabolite levels in normotensive rats.[3] In addition, changes of Pa_{CO_2} of this magnitude would not affect cerebral blood flow in hypotensive animals.[4] Significant metabolic acidosis developed in both groups, with base deficits of 12 ± 1.1 and 8.7 ± 1.6 mEq/l with halothane, 0.6 and 2 per cent, respectively.

Alterations in EEG activity consisted of the appearance of a burst suppression pattern at halothane, 2 per cent, with voltage maintained (fig 1, *a* and *b*), whereas at 0.6 per cent the EEG became nearly isoelectric (<10 μv) in some animals (fig. 2, *a* and *b*). Those rats in which nearly isoelectric EEGs developed had profound depletion of high-energy phosphate values and increases in lactate in cortical tissue from the ligated hemispheres.

With hypotension, the ATP, PCr, and pyruvate values for the right hemispheres (homolateral to the ligated carotid artery) were significantly lower, while ADP and lactate values were significantly higher, with halothane, 0.6 per cent, than the corresponding values with halothane, 2 per cent (table 2). There was no significant difference between cerebral cortical metabolite levels for the left hemispheres in the two groups. Values for the right hemispheres at halothane, 2 per cent, were not significantly different from those for the left hemispheres in both groups.

Discussion

Our results indicate that a decrease in mean arterial pressure to 40 torr induced by infusion of trimethaphan did not cause depletion of brain high-energy stores in ligated hemispheres of rats during deep halothane anesthesia, while it significantly altered the cerebral energy state in ligated hemispheres of rats during light halothane anesthesia (table 2). Changes of cortical tissue high-energy phosphate values of this order of magnitude in this animal model have been shown to be accompanied by neuronal death.[5–6]

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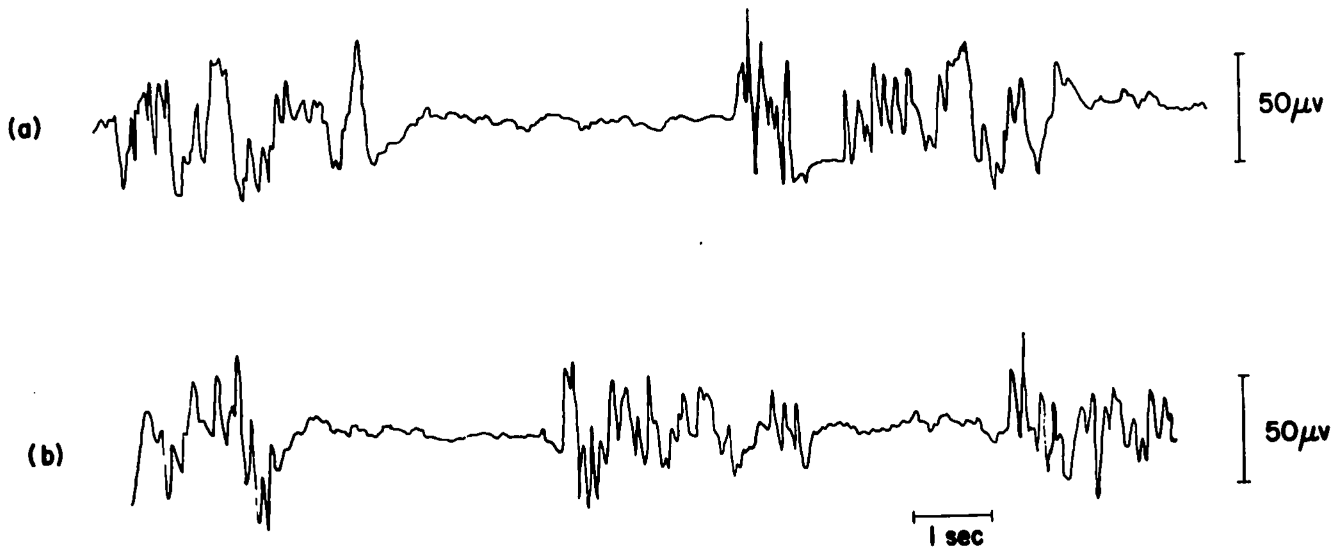

FIG. 1. EEG tracings during administration of halothane, 2 per cent, in oxygen. The pattern of deep anesthesia before hypotension (*a*) was maintained throughout the hypotensive period (*b*).

These findings are in close agreement with those of Nilsson and Siesjö,[7] obtained in rats subjected to profound arterial hypotension to 30 torr produced by halothane, 2 per cent, in oxygen, at Pa_{CO_2} 36 torr. They concluded that hypotension induced by halothane, 2 per cent, produced very small changes in high-energy stores in brain tissue. However, they did not investigate the effects of hypotension upon cerebral cortical metabolite levels during administration of halothane, 0.6 per cent. Differences in cortical tissue metabolite levels between halothane, 0.6 per cent, and halothane, 2 per cent, are far greater on the side of carotid ligation. In cortical tissue from unligated hemispheres there was no detectable difference between metabolite levels with the two anesthetic doses (table 2).

Ransohoff *et al.*[8] adduced evidence that combination of halothane, 2 per cent, and positive airway pressure provided a safe technique for controlled arterial hypotension for surgical occlusion of intracranial aneurysms in man. Arterial hypotension to a level of 30–40 torr systolic facilitated the surgical procedure and gave excellent postoperative results in a group of ten patients. By direct observation of retinal and pial vessels in cats, they determined that this technique was superior to trimethaphan-induced hypotension in terms of cerebral perfusion.

Studies examining hypoxic brain damage during induced arterial hypotension suggest that deep halothane anesthesia preserves aerobic cerebral metabolism during hypotension, while trimethaphan and hypovolemic hypotension result in significant increases in cerebral tissue lactate in dogs.[9] In the same experimental animal, Michenfelder[10] has shown that mar-

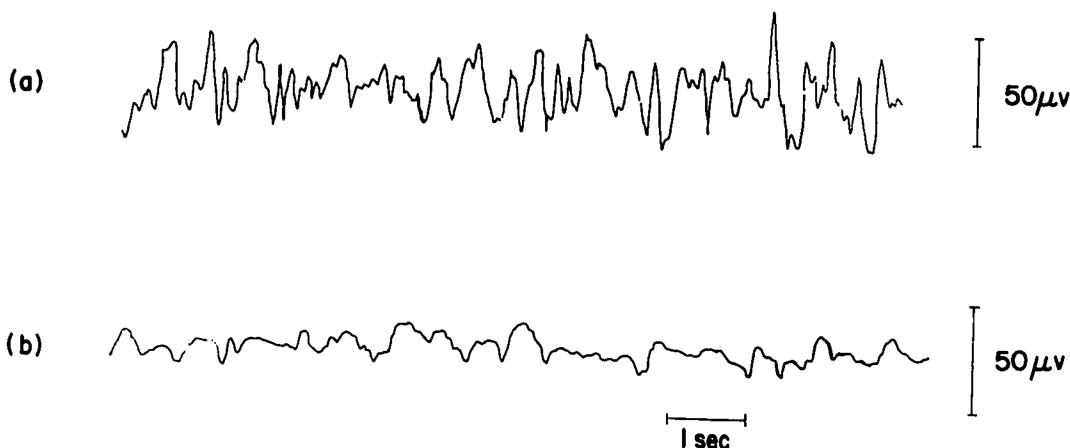

FIG. 2. EEG tracings during administration of halothane, 0.6 per cent. The change from the sleep pattern (*a*) before hypotension to a nearly isoelectric tracing occurred after 5 min of hypotension, and the pattern then remained the same for the rest of the hypotensive period.

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TABLE 2. Cerebral Cortical Tissue Metabolite Levels (μmol/g Wet Weight) from Right and Left Hemispheres after 20 Min of Hypotension during Halothane, 0.6 and 2 per cent (Right Hemispheres Are Homolateral to the Ligated Carotid)

	Right Hemispheres		Left Hemispheres	
	Halothane, 0.6 Per Cent	Halothane, 2 Per Cent	Halothane, 0.6 Per Cent	Halothane, 2 Per Cent
ATP (μmol/g)	1.71 ± 0.05*	2.27 ± 0.02	2.71 ± 0.07	2.71 ± 0.05
ADP (μmol/g)	0.39 ± 0.03*	0.27 ± 0.01	0.32 ± 0.05	0.27 ± 0.01
PCr (μmol/g)	1.97 ± 0.07*	4.01 ± 0.23	3.86 ± 0.17	4.36 ± 0.14
Lactate (μmol/g)	16.5 ± 5.1*	4.75 ± 0.9	3.23 ± 0.64	3.10 ± 0.2
Pyruvate (μmol/g)	0.088 ± 0.01*	0.146 ± 0.018	0.096 ± 0.01	0.116 ± 0.01

All values represent means ± SEM.
Values from right hemispheres were significantly different with halothane, 0.6 per cent, and with halothane, 2 per cent.
* $P < 0.05$.

ginal cerebral perfusion pressure (40 torr) induced by deep halothane anesthesia or nitroprusside infusion in doses of less than 1 mg/kg was better tolerated than similar levels of hypotension produced by trimethaphan or by bleeding.

A direct toxic effect of trimethaphan upon cerebral tissue has been suggested in the past.[11] In our study, the rats exposed to halothane, 0.6 per cent, required significantly more trimethaphan than those exposed to 2 per cent, although no dose–response effect could be seen in individual animals with regard to cerebral cortical tissue metabolites. Metabolite values for unligated hemispheres were identical in the two groups, indicating the absence of a toxic effect of trimethaphan.

In an earlier study by Smith *et al.*[12] examining the extent of cerebral infarction subsequent to ligation of the common carotid and middle cerebral arteries in the dog, severity of infarction was significantly greater in animals undergoing deep halothane anesthesia with or without hypotension than in awake or lightly anesthetized animals. This may have been secondary to the increase in severity of cerebral edema associated with deep halothane anesthesia.[13] In focal ischemia, cerebrovascular effects of halothane may counteract any benefit of decreased cerebral metabolism.

It can be concluded that under the conditions of this study halothane, 2 per cent, appears to afford some protection against brain-tissue ischemia during induced hypotension, while 0.6 per cent does not. It is quite possible that halothane, 2 per cent, decreases CMR_{O_2} to a desirable level, hence protecting cerebral tissue from ischemic insult during induced hypotension.

References

1. Harp JR, Nilsson L, Siesjö, BK: The effect of halothane anaesthesia upon cerebral oxygen consumption in the rat. Acta Anaesthesiol Scand 20:83–90, 1976
2. Lowry OH, Passonneau JV: A flexible system of enzymatic analysis. Brain Res 73:277–289, 1974
3. MacMillan V, Siesjö BK: The influence of hypocapnia upon intracellular *p*H and upon some carbohydrate substrates, amino acids and organic phosphates in the brain. J. Neurochem 21:1283–1299, 1973
4. Okuda Y, McDowall DG, Ali MM, et al: Changes in CO_2 responsiveness and in autoregulation of the cerebral circulation during and after halothane induced hypotension. J Neurol Neurosurg Psychiat 39:221–230, 1976
5. Salford LG, Plum H, Siesjö BK: Graded hypoxia–oligemia in rat brain. I. Biochemical alterations and their implications. Arch Neurol 29:227–233, 1973
6. Salford LG, Plum H, Brierley JB: Graded hypoxia–oligemia in rat brain. II. Neuropathological alterations and their implications. Arch Neurol 29: 234–238, 1973
7. Nilsson L, Siesjö BK: The effect of deep halothane hypotension upon labile phosphate and upon extra- and intracellular lactate and pyruvate concentrations in the rat brains. Acta Physiol Scand 81:508–516, 1971
8. Ransohoff J, Guy HH, Mazzia VDB, et al: Deliberate hypotension in surgery of cerebral aneurism and correlative animal studies. NY State J Med 69:913–918, 1969
9. Yashon D, Stone W, Magness A, et al: Evidence of preservation of aerobic cerebral metabolism during halothane-induced hypotension. J Neurosurg 39:712–717, 1973
10. Michenfelder JD, Theye RA: Canine systemic and cerebral effects of hypotension induced by hemorrhage, trimethaphan, halothane or nitroprusside. ANESTHESIOLOGY 46:188–195, 1977
11. Magness A, Yashon D, Locke G, et al: Cerebral functions during trimethaphan-induced hypotension. Neurology 23:506–509, 1973
12. Smith AL, Hoff JT, Nielsen SJ, et al: Barbiturate protection in acute focal cerebral ischemia. Stroke 5:1–7, 1974
13. Smith AL, Marque JJ: Anesthetics and cerebral edema. ANESTHESIOLOGY 45:64–72, 1976

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