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Anesthetic Effects on Blood–Brain Barrier Function during Acute Arterial Hypertension

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Because anesthetic agents can profoundly alter cerebrovascular tone, they should also influence blood–brain barrier function during acute hypertensive episodes. To investigate this possibility, the authors studied the effects of induced arterial hypertension on penetration of the blood–brain barrier by a protein-bound dye under anesthetic conditions causing cerebral vasoconstriction (sodium thiopental) and vasodilatation (halothane). Forty-eight adult New Zealand white rabbits were anesthetized with nitrous oxide, 70 per cent, oxygen, 30 per cent and pancuronium bromide, 0.8 mg/kg. Ventilation was regulated to maintain Pa_{CO_2} 35 ± 2 torr in 32 animals and 22 ± 2 torr in 16 animals. Either thiopental in repetitive doses (30–60 mg/kg) or halothane was added to decrease mean arterial blood pressure to 40 torr in 3 min. Evans' blue dye (3 per cent, 4 ml/kg) was infused intravenously, after which various doses of norepinephrine were administered to obtain increases in mean blood pressure of 100 to 140 torr in 5–40 sec. After sacrifice of the rabbits, standardized serial coronal sections were examined under incident light for evidence of Evan's blue dye extravasation. Dye passage across the blood–brain barrier was significantly greater ($P < .05$) in rabbits anesthetized with halothane than in those anesthetized with thiopental at both normo- and hypocarbia. Mean dye penetration indices (±SEM) for halothane–normocarbia, halothane–hypocarbia, and thiopental–normocarbia were 21.4 ± 7.9, 9.9 ± 3.8, and 1.5 ± 0.9, respectively. Dye penetration was greatest in grey matter, centered about the lateral sagittal fissure, and tended to spread in the anastomotic zones between major cerebral arteries. In contrast to thiopental, halothane anesthesia appears to enhance the extravasation of plasma proteins into normal brain during acute arterial hypertension, which may contribute to the development of cerebral edema. (Key words: Anesthetics, intravenous: thiopental. Anesthetics, volatile: halothane. Brain: blood–brain barrier; vascular resistance; Blood pressure: hypertension.)

ACUTE ARTERIAL HYPERTENSION produced by the administration of vasopressor drugs disrupts the blood–brain barrier and permits entry of normally excluded plasma proteins into the cerebral interstitial space.[1,2] Papaverine, a cerebral vasodilator, has been shown to potentiate protein entry into the brain during an acute increase in blood pressure.[2] Since anesthetic agents can profoundly alter cerebrovascular tone, they might also influence blood–brain barrier function during acute hypertension. To investigate this possibility, we studied blood–brain barrier function under anesthetic conditions causing cerebrovasoconstriction (sodium thiopental) and cerebrovasodilation (halothane).[3,4]

Method

In 48 adult New Zealand white rabbits (2.5–3.0 kg), anesthesia was induced with halothane, tracheostomy performed, and ventilation then controlled with a volume respirator. Following the placement of arterial and venous catheters, halothane was discontinued and replaced by nitrous oxide, 70 per cent, oxygen, 30 per cent, and pancuronium bromide, 0.8 mg/kg, intravenously. Before termination of halothane anesthesia, lidocaine, 0.5 per cent, was injected into incision sites. During 30 min of stabilization, the ventilator was adjusted to maintain a mean arterial carbon dioxide partial pressure (Pa_{CO_2}) of 35 ± 2 torr (±SEM) in 32 animals; 16 other animals were hyperventilated at Pa_{CO_2} 22 torr. Rectal temperature was maintained at 37 C with a servo-controlled heat lamp.

Either thiopental in repetitive doses (total dose 30–60 mg/kg, intravenously) or halothane (4 per cent inspired) was added to the nitrous oxide anesthesia to decrease mean arterial blood pressures to 40 ± 5 torr in all animals within 3 min. Then Evan's blue dye, a protein-bound dye (3 per cent, 4 ml/kg) was infused intravenously, immediately followed by administration of an individualized bolus dose of norepinephrine to increase blood pressure by 100–140 torr in 5–40 sec. Ouabain, 4 μg/kg, had been given intravenously during the stabilization period to minimize cardiac decompensation from sudden, induced arterial hypertension. Animals (n = 16) developing gross pulmonary edema or arterial oxygen partial pressures of less than 60 torr at $F_{I_{O_2}}$ 0.3 were excluded from the study. Following the vasopressor-induced hypertensive episode, no additional cardiovascular support was given and the blood pressure was allowed to return to control level.

Each animal was sacrificed with an intravenous injection of potassium chloride 30 min after the increase in blood pressure and perfused with physiologic saline solution followed by formalin at an arterial pressure of

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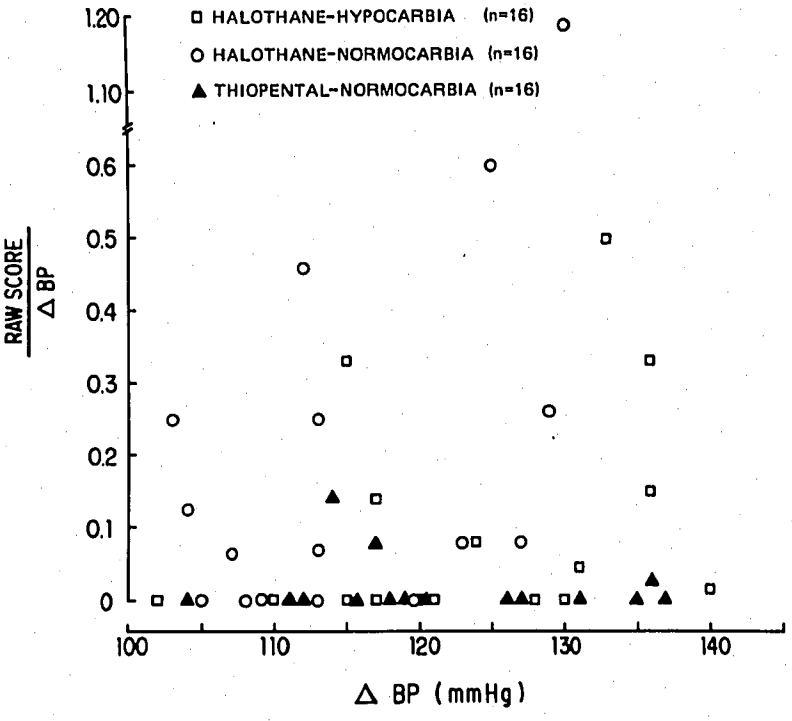

FIG. 1. Effects of rapid change in arterial blood pressure on the dye penetration index (raw score/Δ $\overline{BP}$ × 100) during three anesthetic conditions. Each symbol represents one rabbit.

55 torr via a left ventricular catheter. The brains were removed and stored in formalin for 24 hours. Standardized, serial coronal sections were cut and the brains were examined under incident light for evidence of extravasation of Evan's blue dye. Maps of the extents of subcortical penetration of the dye were drawn from standardized sections placed on a grid network. A raw score for dye extravasation was determined by multiplying the dye-stained tissue, scored (1 to 4) with colorimetric standards, times the area of staining. Mean dye penetration index was calculated as the cumulative raw score for each brain divided by the change in blood pressure × 100. Statistical significance was determined with the t test for unpaired data in all cases, except where comparisons of dye penetration were made. In the latter instance, Wilcoxon's rank sum test was used.[5] $P < 0.05$ was regarded as significant.

Results

Mean blood pressures were decreased to the same extent, approximately 40 torr, in all groups prior to the hypertensive challenge (table 1). The increases in blood pressure in the halothane–hypocarbic and thiopental–normocarbic groups were approximately 122 torr. In the halothane–normocarbic group, the increase was slightly, but significantly, less (115 torr). A significant difference in the dose of norepinephrine necessary to achieve the increase in blood pressure in each group occurred. Mean (±SEM) norepinephrine requirements were: thiopental–normocarbia, 0.04 ± 0.01 mg/kg, halothane–hypocarbia 0.17 ± 0.02 mg/kg, and halothane–normocarbia 0.34 ± 0.02 mg/kg.

Mean dye penetration indices were significantly greater in the halothane–normocarbic and halothane–hypocarbic groups than in the thiopental–normocarbic group (table 1). The extent of dye–protein complex penetration into the brain had a moderate correlation with the increase in blood pressure in the halothane–normocarbic group (fig. 1) (r

TABLE 1. Mean Arterial Blood Pressure Changes and Evan's Blue Dye Penetration Indices Associated with Norepinephrine-induced Hypertension in Rabbits*

	Halothane, Normocarbia (n = 16)	Halothane, Hypocarbia (n = 16)	Sodium Thiopental, Normocarbia (n = 16)
Lowest $\overline{BP}$ (torr)	39.8 ± 1.4‡	41.5 ± 1.3‡	41.4 ± 1.5‡
$\overline{BP}$ increase (torr)	115.0 ± 2.3†	123.6 ± 2.6‡	120.6 ± 2.5‡
Dye penetration index (raw Score/ Δ $\overline{BP}$)	21.4 ± 7.9	9.9 ± 3.8	1.5 ± 0.9†

* Rabbits were anesthetized with halothane or sodium thiopental as shown. The dye penetration index was significantly greater ($P < 0.05$) (Wilcoxon rank-sum test) with halothane (both groups) than with sodium thiopental. Values are means ± SEM.
† $P < 0.05$.
‡ Not significant.

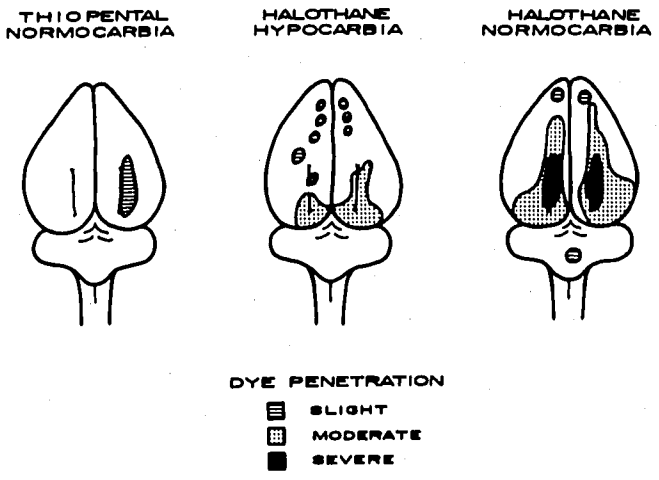

FIG. 2. Cumulative distributions, extents and areas of protein penetration on the dorsal surfaces of the brains after induced arterial hypertension in rabbits during three anesthetic conditions.

= 0.532, $P < .05$). No such correlation was found for the other two groups.

Cumulative extent, distribution, and areas of protein penetration on the dorsal cortical surface of the brain are shown in figure 2. Within each group, protein extravasation was most profound around the lateral sagittal fissure. A progression of increasing intensity and spread of Evan's blue dye staining of the cortex is apparent, with thiopental–normocarbia < halothane–hypocarbia < halothane–normocarbia. Figure 3 demonstrates the neuroanatomic distributions and extents of disruption of the blood–brain barrier in representative coronal sections of brain. In the halothane–normocarbic group, the blood–brain barrier breakthrough occurred mainly in the cortex, with hardly any penetration into white matter. Minimal dye penetration occurred in the thiopental–normocarbia group.

Discussion

Our experiment shows that in the presence of acute hypertension, halothane anesthesia is associated with more protein penetration across the blood–brain barrier than occurs with sodium thiopental. Normally, more than 50 per cent of the aortic arterial pressure head is dissipated in barbiturate-anesthetized animals prior to pial arteriole penetration into the brain.[6] Abnormally high intracapillary pressures could lead to capillary overdistention and rupture of the brain capillary endothelial "tight junctions," which form the morphologic basis for some blood–brain barrier functions. We speculate that the cerebrovasodilation and the loss of cerebral autoregulation due to halothane[7] facilitate the transmission of arterial pressure into the cerebral microcirculation, opening the "tight junctions" and permitting proteins to cross the blood–brain barrier. Supporting this contention is the correlation between the acute change in blood pressure and dye penetration scores in the halothane–normocarbic group (fig. 1). Furthermore, it is conceivable that sodium thiopental, because it maintains autoregulation and has cerebrovasoconstrictive effects, impedes penetration of the arterial pressure head into the microcirculation.

Physicochemical interactions between anesthetic drugs and blood–brain barrier membranes represent another, although less likely, way in which anesthetics could have influenced protein penetration into the brain in our experiment. Distortion of the capillary "tight junctions" by drug adsorption can occur. Rapoport[8] has shown that topically applied agents with high lipid solubilities can cause an irreversible opening of the blood–brain barrier to plasma proteins. Halothane is more lipid-soluble (oil:water = 220) than thiopental (oil:water = 63), and this might contribute to the volatile agent's greater ability to disturb the blood–brain barrier.

The difference between anatomic distributions of protein penetration through the blood–brain barrier in the halothane groups and the thiopental group (figs. 2 and 3) is primarily due to the larger extent of extravasation in the halothane groups. The lateral sagittal fissure area was involved to some extent in all experimental groups. It is a boundary zone between the middle cerebral and posterior cerebral arteries. That these boundary zones are recognized as vulnerable during arterial hypotension appears to introduce a paradox, in that arterial hypertension also causes lesions in the same area. Under our experimental conditions (pharmacologic vasodilation), border-zone capillaries, which normally experience the lowest pressures in the cerebral microcirculation, may suddenly be subjected to very high hydrostatic loads. We suggest that border-zone capillaries may be structurally more fragile than capillary arborizations of major vessels in non-border zones.

Several investigators have demonstrated cerebral hyperperfusion in the areas of blood–brain barrier breakdown due to arterial hypertension during the hypertensive period.[2,9] Later, following normalization of blood pressure, normal or subnormal local cerebral blood flow rates were found in the same regions.[10] Dinsdale suggests that in the latter instance ischemia following acute arterial hypertension could be caused by vasospasm.[9] Formation of cerebral edema in the areas

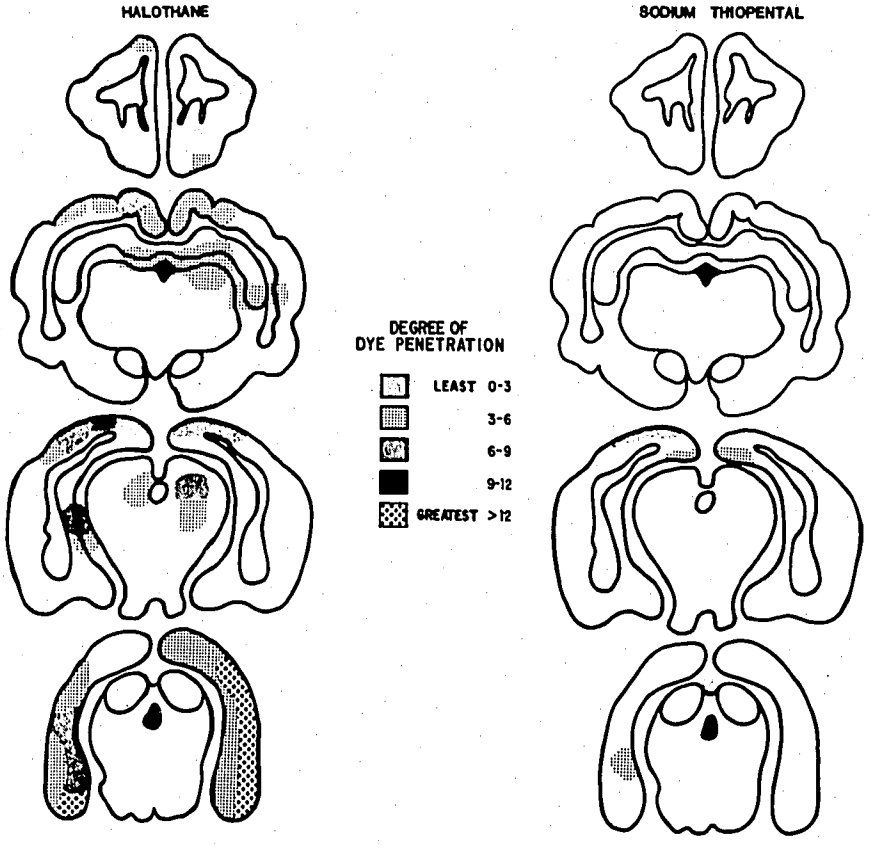

FIG. 3. Cumulative neuroanatomic distributions and extents of blood–brain barrier dysfunction in four representative coronal sections of brains of animals anesthetized with halothane and sodium thiopental during normocarbia.

of dye extravasation could also cause local impairment of cerebral microcirculation. Aside from differences in the anesthetic techniques, and the different doses of vasopressor drug, all three groups were treated the same (table 1). Since norepinephrine, when given by a variety of routes, has been shown to either increase or not affect cerebrovascular resistance,[10] it is unlikely that this is responsible for the blood–brain barrier alterations in our experiment. Dysfunction of the blood–brain barrier can also be caused by arterial hypotension. In our experiment, the decreased mean blood pressure resulting from anesthesia was never less than 35 torr, nor did it remain at this level for more than 30 sec. This extent and transient duration of hypotension should not compromise overall brain oxygenation or cause hypoxia-mediated changes in cerebrovascular and blood–brain barrier function.[11,12]

Most of the previous experiments demonstrating blood–brain barrier breakthrough due to arterial hypertension were performed using barbiturate anesthesia.[1,2] While our experimental design does not permit a statement indicating that sodium thiopental has a protective effect upon blood–brain barrier integrity, our data do indicate that even more severe dysfunction would have been demonstrated in these earlier experiments had volatile anesthetic agents been used.

The issue of whether the increase of cerebral vascular resistance obtained by prior hyperventilation (halothane–hypocapnic group) can ameliorate the deleterious effects of halothane on blood–brain barrier function is not definitely settled. Although no significant difference between the two halothane groups was evident, dye penetration appeared to be less in the hypocapnic group. This observation gains importance because the increase in blood pressure was significantly greater in the hypocapnic group, thus submitting the blood–brain barrier to a greater pressure stress.

Although severe increases in blood pressure such as those shown in our study (100–140 torr) almost never occur in the operating room, abrupt increases in blood pressure of lesser magnitude are common, for example, during aortic cross clamping, during endotracheal intubation, and in the overly zealous treatment of hypotension with vasopressor drugs. In these situations, halothane could potentiate entry of plasma proteins into the brain. This may become increasingly relevant in patients who have suffered trauma to the head or have central nervous system disease, in whom cerebral edema formation could be enhanced. Also, abrupt opening of the blood–brain barrier to plasma proteins could enhance penetration

of the brain by protein-bound drugs and substances that, when toxic levels are reached, can cause further alterations in central nervous system function.

References

1. Haggendal E, Johannson B: On the pathophysiology of the increased cerebrovascular permeability in acute arterial hypertension in cats. Acta Neurol Scand 48:265–270, 1972
2. Johanson B: Blood–brain barrier dysfunction in acute arterial hypertension after papaverine-induced vasodilation. Acta Neurol Scand 50:573–580, 1974
3. Pierce EC Jr, Lambertsen CJ, Deutsch S, et al: Cerebral circulation and metabolism during thiopental anesthesia and hyperventilation in man. J Clin Invest 41:1664–1671, 1962
4. Wollman H: The cerebral circulation during halothane anesthesia, Effect of Anesthetics on the Circulation. Edited by Price HL, Cohen PJ. Springfield, Ill., Charles C Thomas, 1964. pp 209–215
5. Snedecor GW, Cochran WG: Statistical Methods. Sixth edition, Iowa State University Press, Ames, Iowa, 1968, p 130
6. Shapiro HM, Stromberg DD, Lee DR, et al: Dynamic pressures in the pial arterial microcirculation. Am J Physiol 221:279–283, 1971
7. Miletich DJ, Ivankovich AD, Albrecht RF, et al: Absence of autoregulation of cerebral blood flow during halothane and enflurane anesthesia. Anesth Analg (Cleve) 55:100–109, 1976
8. Rapoport SI: Modification of cerebrovascular permeability by hypertonic solutions and conditions which alter autoregulation of cerebral blood flow, The Cerebral Vessel Wall. Edited by Cervos-Navarro J. New York, Raven Press, 1976, pp 215–223
9. Dinsdale HB, Robertson DM, Haas RA, et al: Cerebral blood flow in acute hypertension. Arch Neurol 31:80–87, 1974
10. Olesen J: The effect of intracarotid epinephrine, norepinephrine, and angiotensin on the regional cerebral blood flow in man. Neurology (Minneap) 22:978–987, 1972
11. Fitch W, Ferguson GG, Sengupta D, et al: Autoregulation of cerebral blood flow during controlled hypotension, Cerebral Circulation and Metabolism. Sixth International Symposium on Cerebral Blood Flow. Philadelphia, Springer-Verlag, 1973, pp 18–20
12. Michenfelder JD, Theye RA: Cerebral protection by thiopental during hypoxia. ANESTHESIOLOGY 39:510–517, 1973