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Glucose Transport across the Rat Blood–Brain Barrier during Anesthesia

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The authors studied blood–brain barrier (BBB) glucose transport kinetics in awake rats and in pentobarbital- and halothane-anesthetized rats, using a $^3H_2O/^{14}C$-D-glucose double-indicator method corrected for cerebral blood flow at glucose concentrations from 1 to 80 mM. At normal glucose concentrations (5 mM), total brain glucose influx was unaltered by pentobarbital. In contrast, halothane attenuated glucose transport capacity from 1.9 to 0.4 μmol/g·min^{-1} and increased diffusional transport. K_m (Michaelis constant) was decreased sixfold, from 12 to 2 mM. Halothane appears to inhibit BBB glucose transport by competing for the glucose carrier and by altering the affinity of the carrier for glucose, perhaps by altering the environment of the carrier or the carrier itself. The finding of halothane-induced increased diffusional transport of glucose across the BBB corroborates earlier reports and more recent evidence that halothane increases the permeability of the BBB to diffusional processes. (Key words: Anesthetics, intravenous, pentobarbital; Anesthetics, volatile, halothane; Brain, blood–brain barrier, glucose transport; Metabolism, glucose.)

SEVERAL LINES of evidence suggest that anesthetics may affect glucose transport across the blood–brain barrier (BBB). First, anesthetics affect membrane structure and properties[1–4] that may alter membrane-related functions such as facilitated glucose transport. Second, anesthesia increases the ratio of brain to plasma glucose whether or not plasma glucose is increased,[5,6] which appears to be related to the depth of anesthesia.[7] Mayman *et al.*[5] suggested that the increase in brain–blood glucose during anesthesia is greater than can be accounted for by the decrease in brain glucose metabolism, and may be due to enhanced BBB glucose transport. Data on the effects of anesthetics on BBB glucose transport are sparse. Betz *et al.*[8] concluded that pentobarbital had no effect on BBB glucose transport in the isolated dog brain preparation. Bachelard *et al.*[9] reported no difference in BBB glucose transport kinetics in rats anesthetized with pentobarbital or ether. However, *in vitro*, pentobarbital increased glucose transport in brain slices[10] and halothane decreased CO_2-stimulated glucose transport in erythrocytes.[11]

Briefly, we compared the kinetics of BBB glucose transport during pentobarbital, 60 mg/kg, and halothane, 1.5–2.0 per cent inspired, anesthesia with that in "awake" (post ether anesthetized) rats. Pentobarbital had essentially no effect on BBB glucose transport kinetics, but halothane decreased carrier-mediated transport.

Methods

Wistar female albino rats, 250–400 g body weight, were anesthetized with pentobarbital, 60 mg/kg, intraperitoneally, ether, 15 per cent, or halothane, 5 per cent in O_2. The lungs of rats anesthetized with ether and pentobarbital were mechanically ventilated with nitrogen–oxygen, 50 per cent each, while the lungs of the halothane-anesthetized rats were ventilated with oxygen. The initial studies with halothane were performed using oxygen, and it was presumed that the use of these dissimilar oxygen concentrations would not affect the results. End-tidal CO_2 was continuously monitored (Beckman LB-1 infrared analyzer) and kept at approximately 5–6 per cent. Rectal temperature was kept between 37 and 39 C by an electric blanket. The left common carotid artery was exposed and looped with silk ligatures. A catheter was inserted into the abdominal aorta for mean arterial blood pressure (MAP) monitoring and blood sampling. After surgical preparations, the rats were placed under a guillotine and a 27-gauge needle–catheter inserted nonocclusively into the left common carotid artery for isotope injection. The halothane- and pentobarbital-anesthetized rats were kept anesthetized during study, while the rats anesthetized with ether were allowed to recover from anesthesia until obviously struggling before BBB glucose transport measurements were made.

To measure ^{14}C-D-glucose extraction, a 27-gauge needle–catheter was placed in the left common carotid artery and a 0.2-ml mixture of $^3H_2O/^{14}C$(U)-D-glucose (5 μCi:1 μCi) in Normosol (Abbott Laboratories) at an unlabeled glucose concentration of 1, 5, 10, 20, 40, or 80 mM (pH adjusted to 7.3 by CO_2–HCO_3 buffer and corrected for specific activity of the labeled glucose solution) was injected in 1 sec. Exactly 15 sec after injection, the rats were decapitated. The brains were removed and frozen in dry ice-cooled acetone less than a minute after decapitation. An ar-

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terial blood sample of approximately 1 ml was slowly withdrawn before injection of the isotope for measurement of blood-gas and *p*H values.

Brain tissue was homogenized in water (3:1/water:brain tissue), and 0.2 ml of the brain homogenate assayed for ^{14}C and $^{3}H_2O$ activity by liquid scintillation (Nuclear Chicago). Percentage extraction (E) of ^{14}C-D-glucose was calculated according to the formula:

$$\text{Per cent extraction (E)} = \frac{\dfrac{^{14}C \text{ brain}}{^{3}H_2O \text{ brain (x)}}}{\dfrac{^{14}C \text{ injectate}}{^{3}H_2O \text{ injectate}}} \times 100$$

where x = cerebral blood flow (CBF) correction factor for changes in percentage extraction of $^{3}H_2O$ with changes in CBF.

Oldendorf[12] previously determined that the cerebrovascular clearance time (time for passage of the injected bolus into and out of the cerebral circulation) during pentobarbital anesthesia was approximately 15 sec. Because the cerebrovascular clearance time may be altered by anesthetics, we determined cerebrovascular clearance time of a 0.2-ml bolus of 5 μCi ^{125}I-radioiodinated serum albumin (RISA) injected into a common carotid artery with continuous external scintillation monitoring (2" × 2¼" NaI(Tl), flat-field collimated) of cerebral ^{125}I activity (fig. 1). A straight line was drawn through the curve estimating the postinjection ^{125}I plateau. The first point of intersection of the clearance curve with this line was taken as the clearance time. The time of 15 sec necessary for complete transit of the injected bolus through the brain is about twice the mean transit time of the cerebral circulation for an intravascular tracer, which is about 8 sec.[13]

The Oldendorf $^{3}H_2O$ double-indicator method for estimation of BBB extraction of test substances is based on the assumption that $^{3}H_2O$ is unrestricted in its diffusion across the BBB. However, Raichle *et al.*[14,15] showed that $^{3}H_2O$ penetration across the BBB is restricted, and that cerebral extraction of $^{3}H_2O$ from blood is highly affected by CBF. Bolwig and Lassen[16] determined the relationship between CBF and percentage extraction of $^{3}H_2O$ in the rat brain, thereby allowing the application of correction factors for variations in $^{3}H_2O$ extraction with changes in CBF (fig. 2).

We measured CBF under the conditions of our experiment and the different anesthetic states by continuous external scintillation monitoring of brain ^{133}Xe activity after intra-arterial injection (catheter inserted retrograde into the external carotid artery with the catheter tip at the bifurcation of the internal carotid artery from the common carotid artery) of 100–200 μCi ^{133}Xe in 0.2 ml. CBF was calculated from the recorded clearance curve by the $T_{1/2}$ method, which yields values comparable to calculation by stochastic and compartmental analysis.[17]

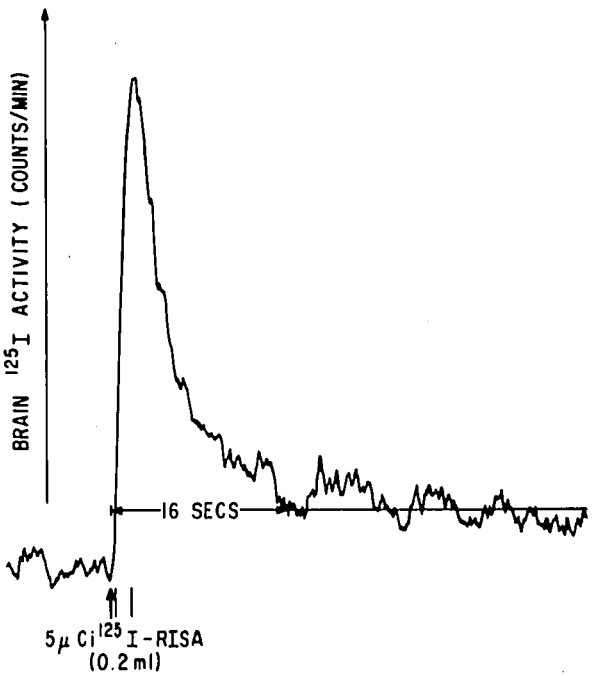

FIG. 1. Determination of cerebrovascular clearance time in a pentobarbital-anesthetized rat. ^{125}I-radioiodinated serum albumin (RISA) was injected into the common carotid artery via 27-gauge needle–catheter with continuous external scintillation monitoring (flat-field collimated) of cerebral ^{125}I activity.

$$\text{CBF (ml/100 g/min)} = \lambda \frac{(\log_e)(60)(100)}{T_{1/2} \text{ (sec)}}$$

Where $\lambda = 1.15$; $T_{1/2}$ = time required for isotope activity to decay to half of peak value in sec.

Arterial blood samples (1.0 ml) were obtained from the catheter in the abdominal aorta as previously described to verify normal acid–base balance before and after CBF measurements. Using the CBF values shown in table 2, correction factors for changes in percentage extraction of $^{3}H_2O$ with changes in CBF during the different anesthetic states were obtained from the data of Bolwig and Lassen.[16] The fraction of $^{3}H_2O$ retained by the brain in a single pass (*i.e.*, 1 − E) is plotted as a function of CBF (fig. 2). The correction factors (x) were used to correct brain extraction fraction of ^{14}C-D-glucose.

Total glucose influx, carrier-mediated transport (CMT) and diffusional transport (DT) were calculated from the data obtained as percentage extraction at each glucose concentration according to the equation. Brain D-glucose influx (μmol/g·min^{-1}) = (E) (G)

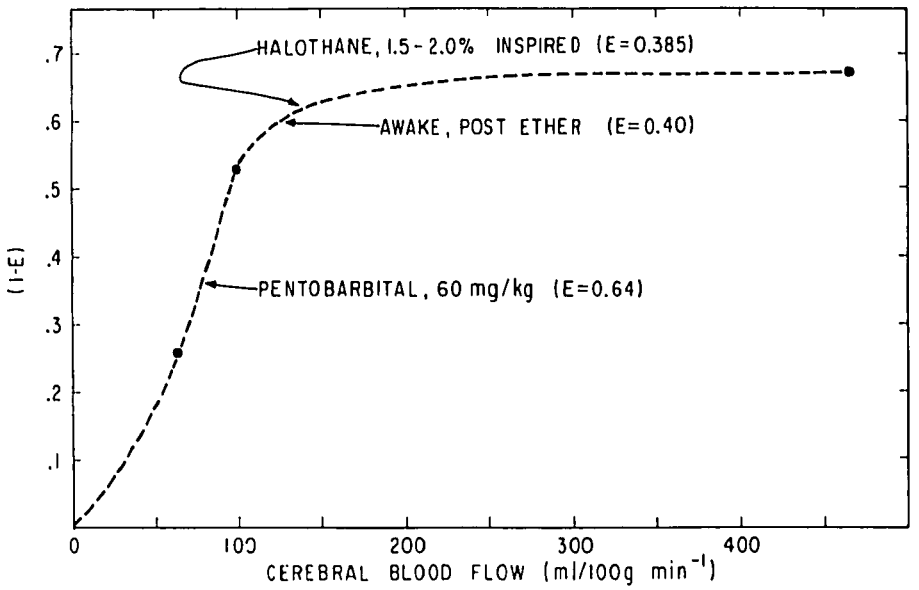

FIG. 2. Relationship between transmitted fraction (1 − E) of ^3H_2O and cerebral blood flow according to the data of Bolwig and Lassen.[16] Extracted fractions (E) in awake and in pentobarbital- and halothane-anesthetized rats were determined using the appropriate cerebral blood flow values. (See table 2.)

(CBF); where: E = CBF-corrected extraction fraction of ^{14}C-D-glucose; G = unlabeled glucose concentration in mM; CBF = cerebral blood flow in ml/g·min^{-1}. The resulting relationship between glucose influx and injectate glucose concentration represents the sum of CMT and DT. To separate the two components of glucose transport (*i.e.*, CMT and DT), the straight-line portion of the curve (presumably representing diffusional transport) was extrapolated to zero glucose concentration and subtracted from the total influx curve to yield CMT of glucose. Maximal glucose transport velocity in μmol/g·min^{-1} (V_{max}) was taken as the plateau value of the CMT curve. The affinity of glucose for the membrane carrier (K_m) was calculated as the reciprocal of the glucose concentration in mM at ½ V_{max}.

All data were analyzed by one-way analysis of variance using F-statistic, with a maximum *P* value of .05 being regarded as statistically significant.

TABLE 1. Effects of Anesthetics on Cerebrovascular Clearance Time

	Clearance (Sec)	Pa_{CO_2} (torr)	Pa_{O_2} (torr)	*p*H$_a$	Base Excess (mEq/l)	Temperature (C)
Awake (post ether)						
$\bar{X}$	15.2	35	94	7.40	−2.7	36.3
SD	0.6	2	19	.03	.6	.4
n	3	3	3	3	3	3
Pentobarbital, 60 mg/kg						
$\bar{X}$	16.2	44	86	7.35	−1.8	36.5
SD	2.7	10	21	.08	−.5	1.8
n*	8	7	7	7	7	2
Halothane, 1.5–2 per cent						
$\bar{X}$	17.7	43	93	7.38	.3	36.5
SD	3.4	3	16	.03	1.2	.1
n	3	3	3	3	3	3

* n = number of rats.

Results

The clearance time for the injected bolus in awake rats was not different from that in rats anesthetized with pentobarbital or halothane rats (table 1). Rectal temperatures, arterial blood gases, and *p*H and base excess values were similar among groups. Pentobarbital decreased CBF 30 to 40 per cent compared with the value for awake rats (table 2). Halothane did not significantly increase CBF above awake levels, but mean CBF was about 10 per cent higher despite a 45 per cent decrease in MAP. The corresponding correction factors (x) for CBF on brain extraction of ^3H_2O in awake and in pentobarbital- and halothane-anesthetized rats were 0.40, 0.64, and 0.385, respectively (fig. 2).

Physiologic variables in awake and in pentobarbital- and halothane-anesthetized rats in which BBB glucose transport was determined were essentially the same and within normal limits within and between the different groups. In both awake and halothane-anesthetized rats extraction of ^{14}C-D-glucose was about 9.5 per cent at an unlabeled glucose concentration of 1 mM (fig. 3). In awake rats, it gradually decreased with increasing glucose, while in halothane-anesthetized rats, it decreased rapidly between 1 and 20 mM glucose, then appeared to plateau between 20 and 80 mM. The percentage extraction during pentobarbital anesthesia was greater than in awake or halothane-

anesthetized rats. At 1 mM glucose, extraction was 21 per cent; it decreased rapidly when glucose was increased to 20 mM, then decreased linearly between 20 and 80 mM.

In awake rats, K_m was 12 mM (*i.e.*, glucose concentration at ½ V_{max}) and V_{max}, 1.9 μmol/g·min^{-1} (fig. 4). At a normal arterial glucose concentration of approximately 5 mM, or 90 mg/100 ml, brain glucose influx was 0.48 μmol/g·min^{-1}, of which 0.07 μmol/g·min^{-1}, or about 15 per cent, was attributable to diffusional transport. Carrier-mediated transport of glucose was saturated at a glucose concentration of about 40 mM. During pentobarbital anesthesia, BBB glucose transport kinetics was not markedly altered compared with the awake state (fig. 5). There was a negligible increase in K_m from 12 to 14 mM with a small increase in V_{max} from 1.9 to 2.3 μmol/g·min^{-1}. Carrier-mediated glucose transport saturated at 40 mM. At an arterial glucose concentration of 5 mM, diffusional transport (0.07 μmol/g·min^{-1}) accounted for 13 per cent influx (0.52 μmol/g·min^{-1}), similar to that observed in awake rats.

During anesthesia with 1.5–2.0 per cent inspired halothane, brain glucose transport kinetics was markedly altered compared with the awake and pentobarbital-anesthetized states (fig. 6). There was a sixfold decrease in K_m to 2 mM with a fivefold decrease in V_{max} to 0.4 μmol/g·min^{-1} and an increase in the proportion of diffusional to carrier-mediated transport of glucose. At 5 mM glucose, influx rate was 0.54 μmol/g·min^{-1}, of which 0.22 μmol/g·min^{-1}, or 40 per cent, was attributable to diffusional transport. Carrier-mediated glucose transport saturated at a glucose concentration of 10 mM. Despite these alterations in glucose transport kinetics during halothane anesthesia, glucose influx was essentially the same as in awake and pentobarbital-anesthetized rats at concentrations of 10 mM or less.

TABLE 2. Rat Cerebral Blood Flow (CBF) during Anesthesia*

	CBF (ml/100 g·min^{-1})	MAP (torr)	pH_a	Pa_{CO_2} (torr)	Pa_{O_2} (torr)	Temperature (C)
Awake (post ether)						
$\bar{X}$	127	133	7.33	39	326	37.8
SEM	20	11	.03	4	16	.06
n	12	12	6	6	6	12
Pentobarbital, 60 mg/kg						
$\bar{X}$	78‡	111	7.29	40	329	37.7
SEM	7	5	.01	4	18	.03
n†	12	11	6	6	6	12
Halothane, 1.5–2 per cent						
$\bar{X}$	138	72§	7.29	39	203	37.7
SEM	7	5	.05	3	83	.03
n	12	11	6	6	6	12

* ^{133}Xe clearance (focused-collimated scintillation probe) from the brain after intra-arterial injection.

† n = number of observations (four CBF determinations in three rats with blood-gas analyses at start and end of CBF measurements).

‡ Significantly lower ($P < .05$) compared with CBF during awake and halothane-anesthetized states.

§ Significantly lower ($P < .05$) compared with awake value.

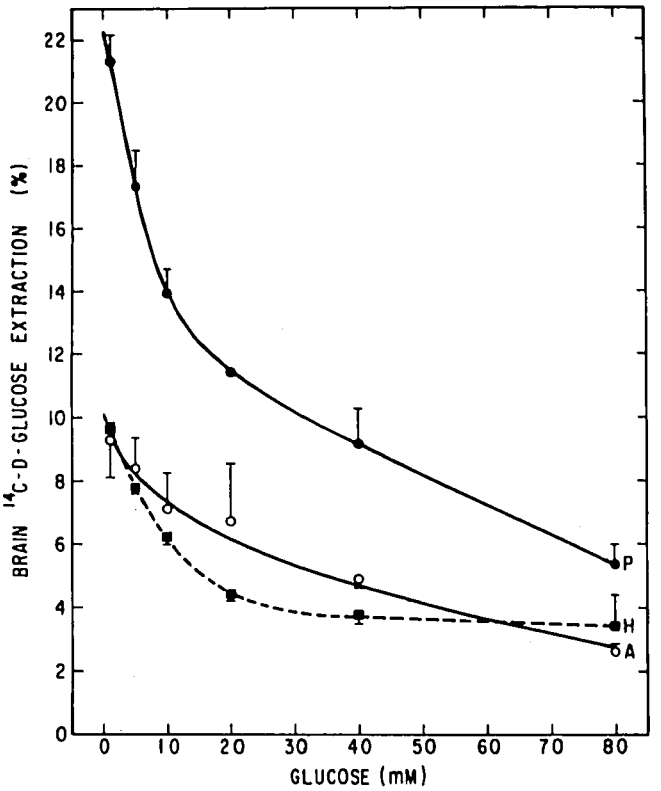

FIG. 3. Cerebral ^{14}C-D-glucose extraction relative to $^{3}H_2O$ extraction (corrected for cerebral blood flow) with increasing unlabeled D-glucose concentrations in the injected boluses in awake (A) and in pentobarbital (P)- and halothane (H)-anesthetized rats. Each point represents the mean ± SEM obtained in four rats except for one point (20 mM glucose) on the pentobarbital curve.

Discussion

Unidirectional glucose transport from blood to brain was not markedly altered by pentobarbital anesthesia compared with the awake state. At normal arterial glucose levels DT in either awake or pentobarbital-anesthetized rats amounted to 15 per cent of total glucose influx, which compares favorably with 16 and 18 per cent reported by Crone[18] and Betz *et al.*,[8] based on BBB fructose diffusion measurements. On the basis of studies of the isolated dog brain preparation, Betz *et al.*[8] concluded that pentobarbital had

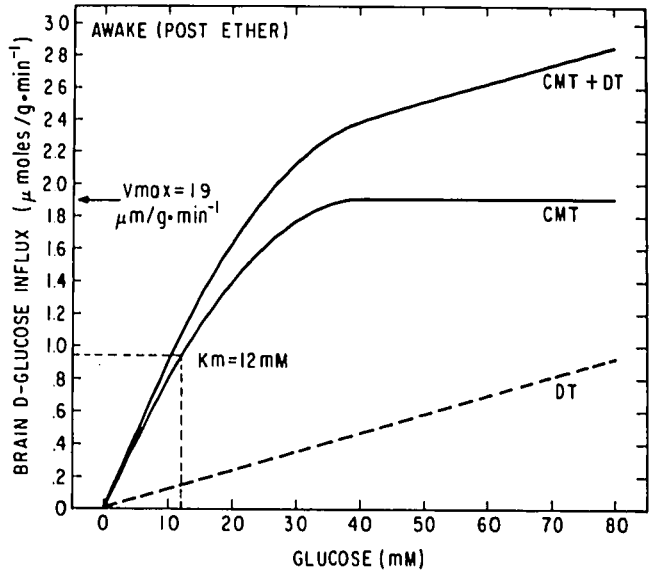

FIG. 4. Blood–brain barrier glucose transport kinetics in awake rats. CMT = carrier-mediated transport. DT = diffusional transport. Curve drawn from data obtained at 1, 5, 10, 20, 40, and 80 mM glucose (n = 24 rats).

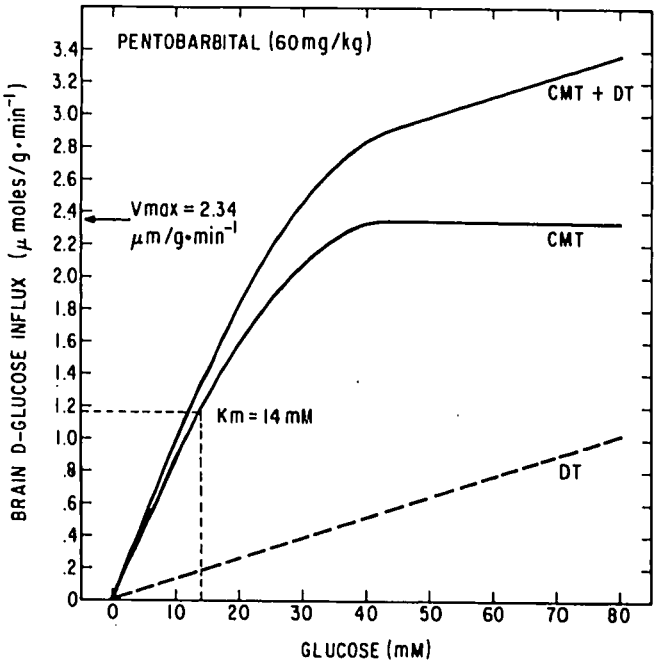

FIG. 5. Blood–brain barrier glucose transport kinetics in pentobarbital (60 mg/kg)-anesthetized rats. CMT = carrier-mediated transport. DT = diffusional transport. Curve drawn from data obtained at 1, 5, 10, 20, 40, and 80 mM glucose (n = 21 rats).

no effect on unidirectional BBB glucose transport with similar V_{max} (1.8 μmol/g·min^{-1}) and K_m (8.4 mM) values in awake and "anesthetized" states. The slightly higher V_{max} we observed during pentobarbital anesthesia compared with post-ether anesthetized rats is probably not important. Our use of steady-state

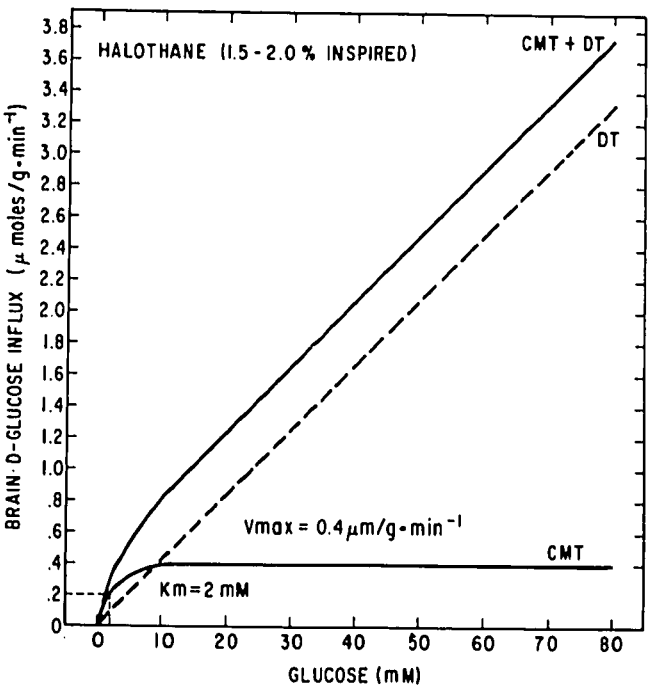

FIG. 6. Blood–brain barrier glucose transport kinetics in halothane (1.5–2.0 per cent inspired)-anesthetized rats. CMT = carrier-mediated transport. DT = diffusional transport. Curve drawn from points obtained at 1, 5, 10, 20, 40, and 80 mM glucose (n = 24 rats).

anesthesia, which increases brain glucose, could lead to an increase in V_{max} because of the increased unlabeled glucose pool in the brain. Indeed, it was specifically to avoid this problem that Betz *et al.*[8] injected pentobarbital intra-arterially (25 mg/l) 20 sec before glucose transport measurements. The wide range of BBB glucose transport kinetic values reported for a variety of anesthetic states and in a number of animal species (K_m = 6 to 9 mM[8,9,20–22] and V_{max} = 1.2 to 3.0 μmol/g·min^{-1} [8,9,22,23]) add further doubt to the significance of the 23 per cent increase in V_{max} we observed during pentobarbital anesthesia.

In contrast to the relatively innocuous effect of pentobarbital on BBB glucose transport, halothane, 1.5 to 2.0 per cent, markedly decreased K_m and V_{max}. The marked decrease in CMT of glucose resulted in carrier saturation at 10 mM instead of 40 mM. Simultaneously, there was a large increase in the DT component, with total unidirectional glucose influx slightly higher at normal arterial glucose than in awake rats. Therefore, halothane markedly inhibited carrier-mediated BBB glucose transport while increasing diffusional permeability to glucose. Greene and Cervenko[11] reported that halothane at clinically effective concentrations of 0.7 to 2.0 per cent significantly inhibited the increase in erythrocytic glucose transport induced by carbon dioxide. Greene and Webb[19] ob-

tained evidence that facilitated transport may be involved in the diffusion of halothane across membranes that may compete with glucose for carrier sites and thereby decrease glucose transport. The marked decrease in BBB glucose transport K_m and V_{max} by halothane we observed also suggests a noncompetitive mechanism of inhibition. The effect of halothane may be to compete with glucose for the carrier and in addition, alter the environment of the carrier or the carrier itself, thereby changing the affinity of the carrier for glucose (*i.e.*, K_m).

A rather unexpected finding is the greater than two-fold increase in DT during halothane anesthesia, suggesting that halothane increases diffusional permeability of the BBB. Angel *et al.*[24] concluded that halothane increased rat BBB permeability to cocaine, but his findings may have also been due to an increase in CBF. Recently, Forster *et al.*[25] reported that during acute hypertension in rabbits, halothane, but not thiopental, increased dye penetration across the BBB. Combined with our findings, there is increasingly greater evidence that halothane increases BBB permeability to substances crossing the BBB by simple diffusion. The mechanism of the increase in permeability is unknown. It may be due to an increase in intravascular pressure at the capillary or precapillary level as a result of cerebrovascular dilation, which opens the endothelial "tight" junctions and thereby increases the passage of solutes across the BBB by simple diffusion. It could also be due to some specific effect of the anesthetic on membrane structure opening the "pores" of the BBB.

All anesthetics tested thus far increase the ratio of brain–plasma glucose two- to threefold.[5,7,26–28] Mayman *et al.*[5] suggested that an increase in BBB glucose transport may be responsible for the increase in the brain–plasma glucose ratio during anesthesia. However, our results showed little, if any, increase in glucose transport by pentobarbital, while halothane decreased CMT, although the increase in DT resulted in a slight increase in glucose influx at normal arterial glucose. Whether these small increases in unidirectional glucose influx during pentobarbital and halothane anesthesia are real and partially account for the increase in the brain–plasma glucose ratio cannot be determined. It is clear, however, that an increase in BBB glucose transport is not a major factor in the process.

An alternative explanation for the increase in the brain–plasma glucose ratio during anesthesia, proposed by Mayman *et al.*,[5] is that glucose may be fairly evenly distributed in total brain water, or that anesthesia alters the compartmentation of glucose within the brain. Both mechanisms are plausible, and they are probably related. The 50 per cent decrease in glucose consumption by the brain during anesthesia would tend to favor a more even distribution of glucose within the brain, thereby decreasing the severity of glucose gradients within different brain regions. The net effect could be an increase in the brain–plasma glucose ratio.

In normal, unanesthetized mouse or rat brain, cerebral metabolic rate for glucose (CMR_G) is about 0.60 μmol/g·min^{-1}, as shown by Lowry *et al.*,[26] Hawkins *et al.*,[29] and Sokoloff *et al.*,[30] using different techniques. It is also well documented that barbiturate anesthesia decreases CMR_G by 40 to 50 per cent, or to about 0.3 μmol/g·min^{-1}.[31] Albrecht *et al.*[32] recently showed that $CMRo_2$ remains depressed by about 20 per cent during emergence from anesthesia and regaining of consciousness. Indeed, the decrease in $CMRo_2$ at subanesthetic levels of ether or cyclopropane anesthesia is greater than at anesthetic levels.[33] With regard to our findings, these data emphasize that (1) CMR_G in awake and anesthetized rats was depressed; (2) the glucose influx rates we observed were probably also depressed somewhat, although the precise extent to which they were depressed cannot be determined since we did not determine CMR_G. However, at arterial glucose levels of about 8 mM, our values for BBB unidirectional glucose influx of 0.7 to 0.8 μmol/g·min^{-1} compare favorably with those obtained by other investigators.[8,9,18,21,23]

Our findings of the effects of halothane on BBB simple diffusion permeability may also be relevant to the effects of anesthetics in the amelioration of ischemic damage to the brain. The effectiveness of barbiturates in decreasing the severity of ischemic cerebral damage sustained after hypoxia–ischemia,[34] focal ischemia,[35,36] and global ischemia (personal communication, Achiel Bleyaert, M.D., Room 1081, Scaife Hall, University of Pittsburgh School of Medicine, Department of Anesthesiology, Pittsburgh, Pennsylvania 15261) have been well documented. However, halothane[35] apparently worsens or, at best, does not affect recovery after focal ischemia. Also, whereas barbiturate anesthetics appear to decrease cerebral edema after cold injury, halothane and enflurane are ineffective.[37] Our results suggest that halothane and perhaps other inhalation anesthetics may increase the permeability of the BBB to water, thereby increasing the propensity for the development of cerebral edema. However, this difference between the barbiturate and inhalational anesthetics remains to be proven.

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