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Title : REDUCED LOCAL TRANSPORT OF ESSENTIAL AMINO ACIDS ACROSS THE BLOOD-BRAIN BARRIER DURING ANESTHESIA

Authors : R. A. Hawkins, Ph.D., A. M. Mans, Ph.D., and J. F. Biebuyck, M.B.Ch.B., D.Phil.

Affiliation: Departments of Anesthesia and Physiology, The Pennsylvania State University, College of Medicine, The Milton S. Hershey Medical Center, Hershey, Pennsylvania 17033

The brain requires a continuous and balanced supply of essential amino acids in order to sustain protein synthesis and to provide substrate for the formation of small polypeptides and certain neurotransmitters, such as serotonin and the catecholamines. The availability of amino acids to brain cells is determined by the transport systems of the blood-brain barrier as well as the plasma amino acid concentrations. Recently, Sage & Duffy (1979) found that the brain uptake indices of several amino acids was altered by pentobarbitone anesthesia and that the effect was different for the various amino acid transport carriers. In a separate study, Anderson et al. (1980) found that halothane reduced the uptake of umbelliferone, a lipid-soluble molecule. These studies raise the question whether and where, within brain, anesthetics influence the transport of important metabolites. Therefore we used phenylalanine (an example of the neutral class of essential amino acids) to study local transport across the blood-brain barrier of many individual brain structures.

Methods. Local amino acid transport was studied using a method recently developed in this laboratory. Briefly, femoral venous and arterial catheters were placed in anesthetized, artificially ventilated rats. Infusion of 14C-phenylalanine was done in such a manner as to rapidly establish and maintain its concentration in arterial blood for 1.5 min whereupon the rat was decapitated and the brain prepared for quantitative autoradiography. Plasma amino acids were measured using an amino acid analyzer. The anesthetics used were halothane 1% in $N_2O{:}O_2$ (70:30), pentobarbitone 50 mg/kg IV, $N_2O{:}O_2$ (70:30) or local anesthetic only (control) group).

Results. The rate of influx of phenylalanine was decreased in all brain areas examined in the anesthetized group as compared to the control group (Table 1). Halothane and pentobarbitone had a greater effect than nitrous oxide, causing decreases of about 15 to 25%. There are three main factors determining the rate of influx of any particular amino acid by this transport mechanism, namely the kinetic characteristics of the carrier; the plasma concentrations of the amino acid and the plasma concentrations of its competitors. Thus, possible alterations in all factors must be considered when changes in influx are found. Both the concentration and the pattern of plasma amino acids were altered during anesthesia (data not shown). In order to take amino acids into account the maximal velocity of the reaction was calculated since this is independent of the concentrations of the substrate and competitors and will therefore reflect only those changes which occur in the transport mechanism. A rearrangement of the Michaelis-Menton equation was used; $V_{max} = v(K_m' + S)/S$. Where: V_{max} = maximal velocity; v = rate of influx; K_m = affinity constant; S = substrate concentration; I = competitor concentration; Ki = inhibition constant; $K_m' = K_m(1 + \Sigma\, I/K_i)$.

When the Vmax values were calculated it became clear that N_2O caused little, if any, change in the transport kinetics. On the other hand, the reduced rate of phenylalanine influx observed with halothane and pentobarbitone appeared to result from both a change in the plasma amino acid pattern as well as an alteration of the transport mechanism.

In summary, halothane and pentobarbitone reduced the rate of essential amino acid influx into brain. This phenomenon may be important to cerebral function during and after anesthesia since in addition to being necessary for protein synthesis, some of the neutral amino acids are direct precursors of neurotransmitters.

References.

1. Sage JI, Duffy TE: Pentobarbital anesthesia: influence on amino acid transport across the blood-brain barrier. Neurochem 33:963-965, 1979.
2. Anderson RE, Michenfelder JD, Sundt TM: Brain intracellular pH, blood flow, and blood-brain barrier differences with barbiturate and halothane anesthesia in the cat. Anesthesiology 52:201-206, 1980.

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TABLE 1. PHENYLALANINE INFLUX IN ALERT AND ANESTHETIZED RATS

	CONTROL	N_2O		HALOTHANE		BARBITURATE	
FRONTAL CORTEX	8.4	7.7	- 8%*	6.5	-22%	6.2	-26%*
CAUDATE	6.6	6.6		5.5	-16%	5.4	-18%
GLOBUS PALLIDUS	5.0	4.7	- 6%	4.1	-18%	4.2	-17%
AMYGDALA	5.9	5.6		5.2	-11%	5.0	-15%
HIPPOCAMPUS	5.7	5.4		4.7	-17%	5.0	-12%
LATERAL SEPTUM	6.4	6.0	- 7%	5.6	-14%	5.5	-14%
HYPOTHALAMUS	7.0	6.2	-11%	5.7	-18%	5.7	-18%
THALAMUS							
ANTERIOR NUCLEI	9.2	8.3	-10%	7.0	-24%	6.9	-25%
VENTRO LATERAL	7.9	7.6		6.6	-17%	6.7	-15%
LATERAL GENICULATE	7.4	7.2		5.8	-21%	6.2	-16%
MEDIAL GENICULATE	8.5	8.1		6.8	-20%	6.8	-20%
SUBSTANTIA NIGRA	7.1	6.5	- 9%	5.7	-20%	5.6	-22%
RETICULAR FORMATION	6.6	6.0	-10%	5.3	-19%	5.3	-20%
SUPERIOR COLLICULUS	8.5	8.3		6.9	-19%	6.8	-20%
INFERIOR COLLICULUS	12.0	11.2	- 7%	8.9	-26%	9.5	-21%
PONS	8.6	8.9		7.6	-11%	6.4	-25%
CEREBELLAR GRAY							
GRANULAR	9.2	8.1	-12%	6.5	-30%	6.7	-28%
MOLECULAR	6.8	6.4	- 7%	6.2	-10%	6.3	- 8%

*All values are expressed in $nmol.min^{-1}.g^{-1}$. Only differences greater than 5% are included.

TABLE 2. CALCULATED LOCAL V_{MAX} OF PHENYLALANINE TRANSPORT

	ALERT	N_2O		HALOTHANE		BARBITURATE	
FRONTAL CORTEX	69	66		61	-12%*	58	-16%*
CAUDATE	54	57	+ 6%*	51	- 6%	50	
GLOBUS PALLIDUS	41	41		39		39	
AMYGDALA	48	48		49		47	
HIPPOCAMPUS	47	46		44	- 6%	47	
LATERAL SEPTUM	53	51		52		52	
HYPOTHALAMUS	58	54	- 7%	54	- 7%	54	- 7%
THALAMUS							
ANTERIOR NUCLEI	76	71	- 7%	66	-13%	65	-14%
VENTRO LATERAL	65	65		62		63	
LATERAL GENICULATE	61	62		55	-10%	58	
MEDIAL GENICULATE	70	69		64	- 9%	64	- 9%
SUBSTANTIA NIGRA	58	56		53	- 9%	52	-10%
RETICULAR FORMATION	54	51	- 6%	50	- 7%	50	- 7%
SUPERIOR COLLICULUS	70	71		65	- 7%	64	- 9%
INFERIOR COLLICULUS	99	95		83	-16%	89	-10%
PONS	70	76	+ 9%	72		60	-14%
CEREBELLAR GRAY							
GRANULAR	76	70		61	-20%	63	-17%
MOLECULAR	56	55		58		59	

*All values are expressed in $nmol.min^{-1}.g^{-1}$. Only differences greater than 5% are included.