Factors in Amino Acid Metabolism Which Can Influence the Central Nervous System

SIDNEY UDENFRIEND, PH.D.*

THE central nervous system, like other organs, obtains its nutrients from the blood stream. The amino acids in the blood are not only those obtained from dietary intake but also those formed by synthetic processes in the liver and kidney. Many amino acids which are not considered as essential to the whole animal are required by the brain and are obtainable only in appropriate quantities when the liver and kidney carry out their synthetic processes normally.

The brain utilizes amino acids for the synthesis of proteins and phospholipids as do other tissues. In addition it requires them for synthesis of many neuroregulatory and special substances, such as noradrenaline, serotonin, melatonin, histamine, acetylcholine and gamma-aminobutyric acid. Synthesis of the pituitary peptides and homocarnosine[1] also makes demands on the amino acid supplies brought to the brain.

MECHANISMS INVOLVED IN AMINO ACID UPTAKE

The mechanisms involved in the uptake of amino acids by the brain are next to be considered in the nutrition of the brain. Consideration of the properties of the "blood-brain barrier" would suggest that amino acids should not be able to penetrate into the brain since they are just the type of water-soluble, charged molecules which are barred entry. However, there is no doubt that amino acids do enter. The rapidity with which L-tyrosine-C^{14} injected into the blood equilibrates with that in the brain is shown in Figure 1. This alone is enough to suggest that amino acids do not penetrate into the brain by mere passive diffusion. However, much direct evidence for catalytic mechanisms for amino acid uptake by the brain has been obtained in a number of laboratories.

In our laboratory we have shown that the uptake of L-tyrosine by the brain, *in vivo*, is rapid and stereoselective (Table 1). Circulating L-tyrosine rapidly attains equilibrium with the brain, whereas p-hydroxyphenylacetic acid, a closely related compound, is excluded totally

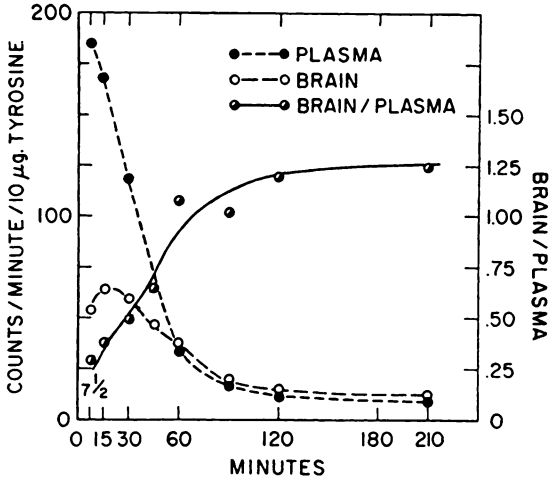

FIG. 1. Distribution of L-tyrosine-U-C^{14} between brain and plasma of rats after its intraperitoneal administration. From CHIRIGOS, M. A., GREENGARD, P. and UDENFRIEND, S. *J. Biol. Chem.*, 235: 2075, 1960.

From the Laboratory of Clinical Biochemistry, National Heart Institute, Bethesda, Maryland.

* Chief, Laboratory of Clinical Biochemistry.

This paper was presented at the Symposium in Memory of Professor Lafayette B. Mendel on Nutrition and Metabolism in Mental Disease, under the sponsorship of The National Vitamin Foundation, Inc., October 6, 1961, Elgin, Illinois.

(Table II). Additional evidence which supports catalytic uptake of amino acids by the brain is the fact that the process is competitive. Tryptophan, leucine, norleucine and fluorophenylalanine when administered along with L-tyrosine markedly inhibit uptake of the tyrosine by the brain, whereas glutamic acid, glutamine and many other amino acids have no effect (Table III). Recent findings in our laboratory indicate that uptake of some amino acids by the brain *in vivo* also shows saturation kinetics characteristic of a catalytic mechanism.[3] These properties of amino acid uptake are not found in all other organs. As shown in Table IV, no competition was observed in the muscle. Thus, the brain contains unique and specific mechanisms for amino acid uptake or transport. One must conclude that the transport apparatus is located in the same areas which make up the "blood-brain barrier."[4] In other words, the brain excludes water-soluble, charged molecules unless they are required nutrients, the latter being taken up at specific catalytic sites. Obviously, similar mechanisms must exist for the entry of nutrients other than amino acids (vitamins, carbohydrates, purines and pyrimidines) into the brain.

CONSEQUENCES OF CATALYTIC MECHANISMS IN THE BRAIN

The presence of such catalytic mechanisms in the brain raises certain questions: (1) Can the transport mechanism limit biosynthetic processes in the brain either normally or under pathologic conditions? Interference with synthesis of neuroregulatory substances derived from amino acids could lead to disturbed physiology. (2) Is it possible that some centrally acting drugs act by influencing transport into the brain? (3) Are peripheral metabolic disturbances more frequently responsible for altered brain function than is now apparent, due to interaction with transport mechanisms? Thus in phenylketonuria the inability of the liver to metabolize phenylalanine results in blood levels of the amino acid which are twenty to forty times normal. Could this huge amount of circulating phenylalanine limit the uptake of tyrosine and other related amino

TABLE I

Distributions of L- and D-Tyrosine between Brain and Plasma after Administration to Rats

Time (min.)	Tissue Levels (μg./ml.)		
	Brain	Plasma	Brain : Plasma
L-Tyrosine (100 mg.)			
15	22	68	0.32
30	44	70	0.63
60	61	64	0.95
120	62	47	1.32
D-Tyrosine (100 mg.)			
15	9	100	0.09
30	16	135	0.12
60	27	119	0.23
120	38	73	0.52

NOTE: The tissue levels in each case were obtained by measuring total tyrosine and subtracting the levels of indigenous L-tyrosine. CHIRIGOS, M. A., GREENGARD, P. and UDENFRIEND, S. *J. Biol. Chem.*, 235:2075, 1960.[2]

TABLE II

Comparison of Uptake of L-Tyrosine and Some Congeners by Brain and Muscle in the Rat

Time (min.)	Tissue Levels (μg./gm.)		
	Brain	Plasma	Muscle
L-Tyrosine (100 mg.)			
15	40	82	46
30	58	77	70
60	75	67	101
120	91	66	87
p-Hydroxyphenylacetic Acid (100 mg.)			
15	0	436	90
30	430	486	136
60	0	416	152
120	0	160	66

NOTE: The gastrocnemius muscle was used in these experiments and homogenized and assayed in the same manner as the brain. The values represent results obtained on individual animals. CHIRIGOS, M. A., GREENGARD, P. and UDENFRIEND, S. *J. Biol. Chem.*, 235: 2075, 1960.[2]

TABLE III

Effect of Amino Acids on the Brain to Plasma Distribution of L-Tyrosine in the Rat

Amino Acid*	Animals Used† (no.)	Amount Administered (mM)	Brain: Plasma	
			30 min.	60 min.
Control	1	...	0.72 ± 0.03	1.04 ± 0.02
L-Tryptophan	4	0.81	0.18	0.31
L-Tryptophan	1	0.26	0.40	0.62
D-Tryptophan	2	0.81	0.42	0.71
β-Fluoro-phenyl-DL-alanine	2	0.81	0.24	0.31
L-Leucine	2	1.14	0.24	0.41
L-Isoleucine	1	1.14	0.28	0.39
L-Valine	1	0.78	0.31	0.47
L-Cysteine	2	0.81	0.37	0.65
L-Histidine	1	0.96	0.38	0.62
L-Alanine	2	1.69	0.88	0.87
L-Serine	1	1.42	0.94	1.22
L-Threonine	1	1.26	0.77	0.81
L-Arginine	1	0.86	0.84	1.49
L-Lysine	1	1.02	0.83	1.04
L-Glutamate	1	1.02	0.81	1.08
L-Glutamine	1	1.02	0.86	1.36

* Amino acids were injected five minutes before injection of 0.55 mM of L-tyrosine.

† When more than one animal was used, average values are given. CHIRIGOS, M. A., GREENGARD, P. and UDENFRIEND, S. *J. Biol. Chem*., 235: 2075, 1960.[2]

TABLE IV

Effect of Other Amino Acids on Tyrosine Uptake

Experiment	Tyrosine Uptake (μg./gm.)	
	Brain	Muscle
L-Tyrosine only	35	53
L-Tyrosine and L-tryptophan	8	68
L-Tyrosine and L-isoleucine	2	53
L-Tyrosine and L-norleucine	15	51
L-Tyrosine and L-glutamic acid	30	52
L-Tyrosine and L-glutamine	35	62

TABLE V

Phenylethylamine Excretion in Phenylketonurics

Subjects	Urinary Excretion of Phenylethylamine (mg./day)	
	No Drug	MAO Inhibitor
Normal	<0.02	0.02
Phenylketonuric patient 1	<0.08	2.8
Phenylketonuric patient 2	<0.02	1.5–2.5

acids, as described? If so, does phenylketonuria represent in fact a nutritional deficiency of certain amino acids in the brain brought on by the phenylalanine competition? Present treatment of patients with phenylketonuria makes use of diets which are sufficiently low in phenylalanine to restore normal blood levels. Would it also be possible to treat patients with phenylketonuria by supplementing the diet with tyrosine, tryptophan and perhaps the leucines to overcome competition with the large amounts of circulating phenylalanine? Maple syrup urine disease[5] is comparable to phenylketonuria in that there is an overabundance of some amino acids in the blood caused by a metabolic disturbance in the liver. In this disorder the blood levels of leucines, valine and methionine are increased markedly.

There are other aspects of brain nutrition which may lead to a pathologic condition. When unusually large amounts of an amino acid are taken up from the blood they may increase metabolism along obligatory pathways in the brain. In phenylketonuria the presentation to the tissues of huge amounts of phenylalanine has been shown to increase the production of phenylethylamine via aromatic L-amino acid decarboxylase[6] (Table v). Since this enzyme also is present in the brain, it is likely that production of the pharmacologically active amine, phenylethylamine, also is increased in the brain. Such an agent may be responsible for some of the central aspects of the disorder.

SUMMARY

Although much is now known concerning the nutritional requirements of the whole animal, relatively little is known concerning the nutritional requirements of individual organs, such as the brain. Obviously normal brain metabolism requires that the blood bring to it certain specific nutrients in proper proportions and that the specific transport mechanisms for each nutrient function properly. The unique nature of the transport mechanism in the brain is an additional factor to consider in evaluating the pathology and pharmacology of the central nervous system.

REFERENCES

1. Pisano, J. J., Wilson, J. D., Cohen, L., Abraham, D. and Udenfriend, S. Isolation of γ-aminobutyrylhistidine (homocarnosine) from brain. *J. Biol. Chem.*, 236: 499, 1961.
2. Chirigos, M. A., Greengard, P. and Udenfriend, S. Uptake of tyrosine by rat brain *in vivo*. *J. Biol. Chem.*, 235: 2075, 1960.
3. Guroff, G., Connamacher, R. and Udenfriend, S. To be published.
4. Guroff, G. and Udenfriend, S. Studies on aromatic amino acid uptake by rat brain *in vivo*. *J. Biol. Chem.*, 237: 803, 1962.
5. Zellweger, H. Amino-aciduria and mental retardation. *Clin. Chem.*, 7: 215, 1961.
6. Jepson, J. B., Lovenberg, W., Zaltzman, P., Oates, J. A., Sjoerdsma, A. and Udenfriend, S. Amine metabolism, studied in normal and phenylketonuric humans by monoamine oxidase inhibition. *Biochem. J.*, 74: 5, 1960.