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Effect of dietary n-3 fatty acid deficiency on blood-to-brain transfer of sucrose, α-aminoisobutyric acid and phenylalanine in the rat

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Possible alterations in blood-to-brain unidirectional transport of sucrose (mol. wt., 342), α-aminoisobutyric acid (mol. wt., 104), and L-phenylalanine (mol. wt., 165) induced by a diet deficient in n-3 polyunsaturated fatty acids were studied with respect to blood–brain barrier function. Two groups of rats were for to two generations with a semisynthetic diet. One group of rats was fed a peanut oil + rapeseed oil diet which contained both essential fatty acids: linoleic acid (18:2 n-6) and α-linolenic acid, (18:3 n-3). Another group was fed a diet of peanut oil, this diet (containing 18:2 n-6) was deficient in α-linolenic acid. The experiments were performed at 6 months of age. Unidirectional transfer rate constants (K_i) of sucrose, α-aminoisobutyric acid and L-phenylalanine were measured. The diet based on peanut oil (deficient in n-3) caused a greater blood-to-brain transport of sucrose but not of α-aminoisobutyric acid or L-phenylalanine. These observations indicate that regardless of the mechanisms involved, alterations in essential fatty acids induced by diet can modulate to some extent the blood–brain transport of hydrophilic molecules without a carrier.

The n-3 and n-6 polyunsaturated fatty acids are essential fatty acid for mammals, because the mammalian tissues lack the Δ^{12}– and Δ^{15}–desaturases necessary to produce linoleic (18:2 n-6) and linolenic (18:3 n-3) acid de novo [25, 28]. Therefore mammals must obtain these fatty acids directly from the dietary sources. The central nervous system (CNS) is more highly enriched than most other tissues in long-chain polyunsaturated fatty acids, and interestingly these fatty acids are practically all structural and are not related to energy production [18, 23]. They participate directly in the architecture, almost exclusively of the structure of membrane phospholipids, and functioning of cerebral membrane [2, 6, 7, 25]. They are the substrates for many biologically active compounds [17, 23] and have a role in some enzymatic activities of brain membranes [3, 6]. In addition they are the major component of excitable membranes and exert a considerable effect on membrane fluidity and the functional properties of certain membrane proteins [23, 25, 26, 27].

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Numerous recent nutritional studies have clearly shown that the n-3 and n-6 polyunsaturated fatty acids are critically important and influence some specific functions of biological membranes [6, 9, 10, 16, 18, 25, 26]. A deficiency of α-linoleic acid in diet alters dramatically the fatty acid composition of various organs including brain [6, 7, 12, 21, 24, 29]. Alterations in the membrane lipid composition of cells can influence carrier mediated membrane transport processes for many substances such as glucose [8], choline, [14] glutamate [1], taurine [31] glycine [30,33] and α-aminoisobutyric acid (AIB) [15] which have been observed to be responsive to polyunsaturated fatty acid supplementations. Moreover, it has been shown that α-linolenic acid deficiency alters n-3 fatty acids in the cerebrovascular endothelium [13] and in other brain cells [7]. It has also been observed that in contrast with the other organs, recuperation from these abnormalities requires many weeks for brain cells [5], brain organelles [32] and especially for brain microvessels [13]. These findings suggest that membrane polyunsaturation may play a role in some transport properties of biological membranes and among them those of cerebrovascular endothelial cell membrane (blood–brain barrier). Since the blood–brain barrier (BBB) is of cru-

cial importance in the transport of the metabolic substrates [11] and since the cerebrovascular endothelium could play an important role in the elongation and desaturation of n-3 and n-6 essential fatty acids during their transfer from circulation into brain [17], the transport characteristics of cerebral microvessels may influence the availability of biologically important compounds for use by the brain. The possibility of such alterations in permeability of cerebral microvessels induced by dietary polyunsaturated fatty acid has not been studied so far. Therefore we investigated the possible effect of dietary n-3 fatty acid deficiency on some transport characteristics of the BBB. An abstract of this work has already been published [35].

Two groups of Sprague–Dawley rats (from Iffa Credo, France) were used. One was fed for two generations with a semi-synthetic diet containing peanut oil (18:2 n-6). The other received peanut oil + rapeseed oil (18:2 n-6 + 18:3 n-3). The mixture peanut oil + rapeseed oil was chosen as it provides minimum amounts of both essential fatty acids as indicated in Table I. The diets differ mainly by their n-3 and n-6 fatty acid content. The experiments were performed when the animals were 6 months old.

The regional blood-to-brain transfer of sucrose, AIB and L-phenylalanine was determined with the [^{3}H] or [^{14}C] form of these compounds. [^{3}H]L-phenylalanine (3.7–4.8 TBq/mmol) and [^{14}C]sucrose (17–24.4 GBq/mmol) were obtained from Amersham International (UK). [^{3}H]AIB (1239 GBq/mmol) was obtained from New England Nuclear (Boston, MA, USA).

TABLE I

DIET COMPOSITION

[1]United States Biochemical Corp., Cleveland, OH. Composition of vitamin supplement g/kg (triturated in dextrose): -tocopherol (1000 IU/g) 5.0, L-ascorbic acid 45.0, choline chloride 75.0, D-calcium pantothenate 3.0, inositol 5.0, menadione 2.25, niacin 4.5, para-aminobenzoic acid 5.0, pyridoxine HCl 1.0, riboflavin 1.0, thiamin HCl 1, retinyl acetate 900,000 IU, ergocalciferol (vitamin D_2) 100,000 IU; composition in mg/kg: biotin 20, folic acid 90, vitamin B_{12} 1.35.

[2]Composition of the mineral mixture (per kg on diet): $CaHPO_4 \cdot 2H_2O$ 15.2, K_2HPO_4 9.6, $CaCo_3$ 7.2, NaCl 2.8, MgO 0.8, $MgSO_4 \cdot 7H_2O$ 3.6, $FeSO_4 \cdot 7H_2O$ 0.28, $ZnSO_4 \cdot 7H_2O$ 0.2, $MnSO_4 \cdot H_2O$ 0.2, $CuSO_4 \cdot 5H_2O$ 0.04, NaF 0.04, $Al_2(SO_4)3K_2SO_4 \cdot 24H_2O$ 0.008, KI 0.0032, $CoCO_3$ 0.0032, $Na_2SeO_3 \cdot 5\ H_2O$ 0.0004.

Ingredient	Rapeseed + peanut (g/kg diet)	Peanut (g/kg diet)
Casein (delipidated)	220	220
DL-Methionine	1.5	1.5
Cellulose	20	20
Starch	435.5	435.5
Saccharose	218	218
Peanut oil	25	50
Rapeseed oil	25	0
Vitamin mixture[1]	10	10
Mineral mixture[2]	45	45

For L-phenylalanine, 370 kBq of tritiated L-phenylalanine were injected i.v. per animal, blood was regularly collected by syringe and the animal was decapitated 20 s after injection. For the substances with a slow penetration (sucrose and AIB) details of animal preparation and calculations for determination of BBB integrity have already been reported [36]. To summarize: 0.5 ml isotonic saline containing 185 kBq [U-^{14}C]sucrose and 625 kBq [^{3}H]AIB was injected intravenously. Blood samples (100–200 μl/sample) were collected periodically from the femoral artery until the rat was decapitated 10 min after injection of the radiotracers. The brain was quickly removed from the skull and dissected into specific regions. Whole blood, arterial plasma and weighed regions of the brain were prepared for counting of radioactivity as previously described [36]. The amount of each tracer in both blood and brain was measured using a liquid scintillation counter (Intertechnique SL 3000).

Regional blood-to-brain transfer constants were calculated from the tissue and plasma radioactivity data using the following equation originally developed by Ohno et al. [19]:

$$K_i = \frac{(C)_{br}(T) - V \cdot C_{wb}(T)}{\int_0^t C_{pl}\,dt} \quad [1]$$

where C_{br} is the amount of tracer in the brain per unit mass of tissue (dpm/g) at time T, T is the duration of experiment (min), C_{pl} is the arterial plasma concentration (dpm/ml), V is the regional blood volume, and C_{wb} is the tracer concentration in blood obtained at decapitation (dpm/ml).

In experiments with sucrose and AIB, regional blood volume (V in the formula) was determined for the [^{14}C]sucrose space and corresponds to the ratio:

$$\frac{\text{dpm/g brain}}{\text{dpm/ml whole blood}} \times 100$$

at the time of death, 2 min after injection of sucrose. Since sucrose passes the BBB at a very slow rate, it can be considered to be restricted to cerebral vessel during the first 2 min unless the BBB has been disrupted. Radioactivity was determined in whole blood and brain samples as described above. In experiments with phenylalanine, the regional blood volume was also determined from the distribution space of sucrose, at the same time as decapitation, i.e. at 20 s.

Student's t-test was used to compare means for peanut oil fed rats and peanut oil + rapeseed oil fed rats. One-way analysis of variance was used to compare the treatment groups, followed by Student's t-test when overall difference was significant. Significance was taken as $P<0.05$.

Cerebrovascular space values measured for sucrose were found to be similar in both animal groups and ranged from 2.38% (bulb olfactorius) to 1.03% (striatum). These values are in agreement with previously published results in control rats [19, 34].

The unidirectional transfer constant (K_i) values for L-phenylalanine calculated in the different brain regions by equation [1] are shown in Table II. The values for phenylalanine transport did not differ in any brain region studied in the two experimental groups.

The K_i values for sucrose (Table III) transport were twofold higher in certain gray matter areas in rats fed peanut oil than in rats fed peanut oil + rapeseed oil. No detectable differences in white matter uptake of [^{14}C]sucrose were found between the two groups of animals.

The K_i value for AIB (Table III) differed slightly but only in parietal cortex, superior colliculus, and thalamus in rats fed peanut oil + rapeseed oil compared to those fed peanut oil. In the rest of the brain regions K_i values were found to be similar in both animal groups.

The cerebrovascular endothelial cells are joined together by tight junctions. Therefore they form a continuous cell layer between blood and brain [22]. The transcapillary movement of solutes is hindered by this cellular membrane [11]. The rate of blood–brain exchange is relatively low for water-soluble extracellular substances that have no carrier (such as sucrose). The passage through the BBB occurs mainly by dissolving in and diffusing through the membranes and cytoplasm of endothelial cells, and consequently depends on the lipid solubility [11]. However, the transport of certain water-soluble compounds (such as phenylalanine) across the BBB is facilitated by a carrier system located in the luminal and abluminal membranes of endothelial cells [20].

Since the lipid composition of brain microvessels has been shown to be modified by diet [13] and since the fact that the passage of substances through a cell membrane can occur by simple diffusion or by carrier systems, we studied the transport of 3 water-soluble substances across the BBB which is similar in permeability to that of a cellular membrane because of the presence of tight junctions between the cells: (a) sucrose does not have a carrier system, (b) AIB is probably transported by ordinary diffusion, but has carriers at the abluminal membrane of endothelial cells, at the meningeal and brain cell membranes, (c) L-phenylalanine is a neutral amino acid and has a carrier system at the luminal membrane of endothelial cells.

Since sucrose and AIB transport is slow, the measurement of blood-to-brain transport was determined 10 min after injection of tracers to accumulate sufficient radioactivity for accurate measurement. To test for linearity of uptake at this time, experiments were conducted at 5 and 10 min and the results obtained provided evidence that accumulation of label was a linear function and that backflux does not occur before 10 min (data not given here).

The results obtained in the present study indicate that blood-to-brain transport of sucrose was similar to published values in rats fed rapeseed + peanut oil. This transfer was increased in gray matter areas but was not markedly changed in white matter areas in rats fed with a diet sufficient in linoleic but deficient in α-linolenic acid, while transport of AIB was similar in both groups.

These different uptake profiles in the transport of sucrose and AIB can be explained by the rapid uptake of AIB by brain and meningeal cells. Although the influxes of sucrose and AIB across the BBB are relatively slow and without carrier mediated transport, the brain cells and arachnoid cells have transport systems for AIB and these cells rapidly take up and accumulate AIB once it has passed across the BBB into the interstitium of the brain [4]. Because meningeal cells were already eliminated during dissection, their contribution for AIB transport was not taken into account.

TABLE II

REGIONAL BLOOD TO BRAIN TRANSFER CONSTANT (K_i) FOR L-PHENYLALANINE IN RATS FED PEANUT OIL + RAPESEED OIL (NON-DEFICIENT DIET) OR PEANUT OIL ONLY (α-LINOLENIC DEFICIENT DIET)

Values are mean ± SEM (n = 4). The K_i was calculated by Equation 1. Rats were decapitated 20 s after injection of tracers. There were no significant differences between the two groups ($P<0.05$).

	K_i (ml·g^{-1}·min^{-1})	
Brain region	Rapeseed + peanut	Peanut
Olfactory bulbs	0.150 ± 0.023	0.199 ± 0.084
Hypothalamus	0.133 ± 0.016	0.124 ± 0.014
Frontal cortex	0.146 ± 0.024	0.140 ± 0.035
Parietal cortex	0.128 ± 0.059	0.142 ± 0.022
Occipital cortex	0.137 ± 0.025	0.135 ± 0.023
Striatum	0.104 ± 0.014	0.104 ± 0.025
Hippocampus	0.117 ± 0.019	0.108 ± 0.016
Thalamus	0.123 ± 0.017	0.114 ± 0.014
S. colliculus	0.148 ± 0.022	0.153 ± 0.025
I. colliculus	0.157 ± 0.019	0.162 ± 0.041
Midbrain	0.118 ± 0.011	0.111 ± 0.019
Pons-medulla	0.126 ± 0.009	0.115 ± 0.020
Cerebellum	0.137 ± 0.018	0.150 ± 0.016
White matter	0.106 ± 0.029	0.100 ± 0.024

TABLE III

REGIONAL BLOOD TO BRAIN TRANSFER CONSTANT (K_i) FOR AIB AND SUCROSE IN RATS FED PEANUT OIL + RAPESEED OIL (NON-DEFICIENT DIET) OR PEANUT OIL ONLY (α-LINOLENIC DEFICIENT DIET)

Values are means ± S.E.M.; n = 4–6. The K_i was calculated by Equation [1]. Animals were decapitated 10 min after injection of tracers.

	K_i (ml·g^{-1} min^{-1}·10^3)			
	AIB		Sucrose	
Brain region	Rapeseed+peanut	Peanut	Rapeseed+peanut	Peanut
Olfactory bulbs	3.29 ± 0.54	3.61 ± 0.36	0.68 ± 0.14	1.61 ± 0.47*
Hypothalamus	3.50 ± 0.10	3.04 ± 0.26	0.74 ± 0.06	1.05 ± 0.09*
Frontal cortex	2.55 ± 0.07	2.23 ± 0.38	0.54 ± 0.05	0.88 ± 0.09*
Parietal cortex	2.68 ± 0.07	2.94 ± 0.29	0.54 ± 0.05	1.05 ± 0.05*
Occipital cortex	2.48 ± 0.11	2.68 ± 0.45	0.54 ± 0.05	1.06 ± 0.17*
Striatum	2.16 ± 0.07	2.08 ± 0.13	0.48 ± 0.05	0.85 ± 0.05*
Hippocampus	2.16 ± 0.28	2.03 ± 0.27	0.50 ± 0.07	0.88 ± 0.20*
Thalamus	2.17 ± 0.07	1.77 ± 0.18*	0.65 ± 0.07	0.95 ± 0.06*
S. colliculus	2.52 ± 0.13	1.91 ± 0.25*	1.00 ± 0.09	1.85 ± 0.40*
I. colliculus	2.38 ± 0.29	2.63 ± 0.37	0.93 ± 0.14	1.71 ± 0.27*
Midbrain	1.92 ± 0.03	2.13 ± 0.21	0.93 ± 0.14	1.71 ± 0.27*
Pons	1.98 ± 0.14	2.29 ± 0.44	0.57 ± 0.05	1.11 ± 0.25*
Medulla	2.64 ± 0.17	2.64 ± 0.13	0.77 ± 0.04	1.28 ± 0.20*
Cerebellum	2.67 ± 0.15	2.75 ± 0.20	0.55 ± 0.07	0.92 ± 0.25*
White matter	2.09 ± 0.20	2.12 ± 0.31	0.76 ± 0.19	1.27 ± 0.27

*Significant difference (P<0.05) between rats fed peanut oil + rapeseed oil and rats fed peanut oil.

The effect of fatty acids on carrier mediated transport has been slightly more studied than passage by simple diffusion in other organs, but a few studies have evaluated such transport in brain. In some of these studies, it has been shown that unsaturated fatty acids inhibit the Na^+ dependent uptake of several amino acid neurotransmitters including glutamate, aspartate, γ-aminobutyric acid (GABA) and glycine. Two other investigators have also reported that the Arrhenius plot of intestinal transport of glucose [8] and transport of glycine in glial cells [33] shows a break point which indicates that there is a phase change (gel-liquid crystal) in the membrane. Studies have been done by modification of the diet [9,10] or on cultured cells [1,15,30,31] to which unsaturated fatty acids have been added to the fetal serum, the only source of fatty acids. In our study we evaluated the tracer uptake of L-phenylalanine and we found that the uptake of L-phenylalanine appeared to be unchanged in rats fed the different fatty acid diets. These observations are in agreement with a previous study in which no changes in leucine transport (which is in general transported by the same carrier system as phenylalanine) were observed as a result of modification of fatty acid content in cultured retinoblastoma cells [31].

Although no modification in the carrier mediated transport system occurred, our results indicate that dietary modification of α-linoleic acid in some degree may alter the diffusion characteristics of cerebrovascular endothelial cell membranes (BBB) to water-soluble molecules that do not have a carrier. The mechanism of this change is not known but it is most likely that dietary modification of unsaturated fatty acids may directly act on the lipid domain of the membrane and produce significant changes in the packing of the lipid molecules as suggested by some authors [33].

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