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Prostaglandins Leukot Essent Fatty Acids. Author manuscript; available in PMC 2009 August 12.

Published in final edited form as:
Prostaglandins Leukot Essent Fatty Acids. 2007 ; 77(5-6): 251–261. doi:10.1016/j.plefa.2007.10.023.

Brain metabolism of nutritionally essential polyunsaturated fatty acids depends on both the diet and the liver

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Abstract

Plasma α-linolenic acid (α-LNA, 18:3n-3) or linoleic acid (LA, 18:2n-6) does not contribute significantly to the brain content of docosahexaenoic acid (DHA, 22:6n-3) or arachidonic acid (AA, 20:4n-6), respectively, and neither DHA nor AA can be synthesized *de novo* in vertebrate tissue. Therefore, measured rates of incorporation of circulating DHA or AA into brain exactly represent the rates of consumption by brain. Positron emission tomography (PET) has been used to show, based on this information, that the adult human brain consumes AA and DHA at rates of 17.8 and 4.6 mg/day, respectively, and that AA consumption does not change significantly with age. In unanesthetized adult rats fed an n-3 PUFA "adequate" diet containing 4.6% α-LNA (of total fatty acids) as its only n-3 PUFA, the rate of liver synthesis of DHA is more than sufficient to replace maintain brain DHA, whereas the brain's rate of synthesis is very low and unable to do so. Reducing dietary α-LNA in an DHA-free diet fed to rats leads to upregulation of liver coefficients of α-LNA conversion to DHA and of liver expression of elongases and desaturases that catalyze this conversion. Concurrently, the brain DHA loss slows due to downregulation of several of its DHA-metabolizing enzymes. Dietary α-LNA deficiency also promotes accumulation of brain docosapentaenoic acid (22:5n-6), and upregulates expression of AA-metabolizing enzymes, including cytosolic and secretory phospholipase A_2 and cyclooxygenase-2. These changes, plus reduced levels of brain derived neurotrophic factor (BDNF) and cAMP response element-binding protein (CREB), likely render the brain more vulnerable to neuropathological insults.

Keywords

docosahexaenoic acid; liver; brain; rat; n-3 PUFAs; imaging; metabolism; phospholipase A_2; BDNF; diet; arachidonic acid

1. Introduction

Brain structure and function, particularly neurotransmission, depend on interactions between arachidonic acid (AA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3) at multiple target sites [1–6]. These long-chain polyunsaturated fatty acids (PUFAs) and their respective shorter-chain PUFA precursors, linoleic acid (LA, 18:2n-6) and α-linolenic acid (α-LNA, 18:3n-3), are nutritionally essential and cannot be synthesized *de novo* in vertebrate tissue [7].

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September 11, 2007 For Prostaglandins other Lipid Mediators, Quebec Conference

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Animal studies with different proportions of PUFAs in the diet have identified broad dietary requirements for maintaining optimal brain function [8], and have demonstrated that metabolic and behavioral defects arise from severe long-term n-3 PUFA dietary deprivation. Additionally, clinical studies indicate that low dietary consumption of n-3 PUFAs or a low plasma DHA concentration is correlated with a number of brain diseases and with cognitive and behavioral defects in development and aging [9–11], and that dietary n-3 PUFA supplementation may be beneficial in some of these conditions [6, 12].

Effects on the brain of minor n-3 PUFA dietary deprivation associated with small declines in plasma DHA concentrations of the order found in the clinic have rarely been studied in animal models. Additionally, controversy exists about which dietary PUFA compositions are optimal for human brain function [6, 12–16]. The liver's *in vivo* capacity to convert α-LNA or eicosapentaenoic acid (EPA, 20:5n-3) to DHA, or LA to AA, has not be quantified in animals or in humans, although changes in this capacity with development, aging or disease likely impact brain PUFA metabolism [17–21].

Several important questions regarding the relation of brain PUFA metabolism to diet and liver PUFA metabolism have recently been partially resolved, and we shall discuss them in this brief review. These are: (1) What are the rates of brain consumption of AA and DHA in rats and humans? (2) How does brain DHA metabolism depend on dietary n-3 PUFA composition and the liver's ability to convert α-LNA to DHA? (3) How do brain lipid enzymes and trophic factors respond to dietary n-3 PUFA deprivation?

We have developed kinetic methods and models to address these questions in the intact awake organism. The methods include brain imaging with quantitative autoradiography or positron emission tomography (PET), intravenous injection of radiolabeled PUFAs to examine incorporation, turnover and synthesis rates of PUFAs in brain or liver, enzyme assays to evaluate activities of lipid metabolizing enzymes, and molecular techniques to examine transcriptional regulation and protein levels of these enzymes.

2. Methods and Models

AA and DHA are found in high concentrations in the stereospecifically numbered (*sn*)-2 position of brain membrane phospholipids, from where they can be released by selective phospholipase A_2 (PLA_2) enzymes 1, 22–27. After release, most of the unesterified AA or DHA will be rapidly reincorporated into an unesterified *sn*-2 position in a lysophospholipid *via* the acyl-CoA pool, through serial actions of an acyl-CoA synthetase and acyltransferase with the consumption of two molecules of ATP [28]. A small fraction, however, will be lost through any of a number of catabolic pathways, including β-oxidation and conversion to eicosanoids or docosanoids by cyclooxygenases (COXs), lipoxygenases, or cytochrome P450 [29–33].

Figure 1 illustrates major pathways that DHA can take after it is released from phospholipids by activation of PLA_2; a similar figure exists for the AA cascade 3, 27, 34. The figure identifies two ways in which brain turnover of DHA (or AA) can be considered [35]. The first is deacylation followed by rapid reacylation into phospholipid [30, 36], a process which is associated for both DHA and AA with neurotransmission *via* receptors that are coupled to PLA_2 [1, 2, 37]. The second relates to the net loss of DHA from brain, followed by its replacement by plasma unesterified DHA. It turns out that the rate of replacement of AA or DHA, J_{in} in Figure 1 (entry arrow) exactly equals the rate of loss (sum of small arrows to β-oxidation and docosanoids and other catabolic pathways not shown), because the circulating precursors LA and α-LNA, do not contribute significantly (< 1% converted) to brain AA or DHA, respectively (e.g. Figure 2),

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and neither AA nor DHA can be synthesized *de novo* in vertebrate tissue [7, 38, 39]. Replacement occurs independently of changes in cerebral blood flow [31, 40, 41].

3. Results and modeling

Equations for incorporation rates and half-lives

We can quantify J_{in} for AA or DHA by infusing intravenously albumin-bound radiolabeled PUFA in an organism, then imaging regional brain radioactivity in frozen brain, or determining radioactivity in individual stable lipids (phospholipids, triacylglycerols and cholesteryl esters) in high-energy microwaved brain [1, 37].

For imaging, we first determine an incorporation coefficient k^* (ml/sec/g brain) using quantitative autoradiography or PET following the intravenous injection of the labeled AA or DHA, by dividing regional brain radioactivity by the integrated plasma radioactivity (input function),

$$k* = \frac{c^*_{brain}(T)}{\int_0^T c^*_{plasma} dt} \qquad \text{(Eq. 1)}$$

where t is time after beginning tracer infusion, $c^*_{brain}(T)$ nCi/g is brain radioactivity at time T of sampling (often 5 min), and c^*_{plasma} nCi/ml is plasma radioactivity. Then, J_{in} nmol/sec/g brain is calculated by multiplying k^* by the unlabeled unesterified plasma AA or DHA concentration, c_{plasma} nmol/ml,

$$J_{in} = k * c_{plasma} \qquad \text{(Eq. 2)}$$

The half-life for net loss of the PUFA from brain is given as follows, where the unlabeled PUFA concentration in net brain stable lipid (mainly phospholipid) equals c_{brain} nmol/g,

$$t_{1/2} = 0.693\, c_{brain} / J_{in} \qquad \text{(Eq. 3)}$$

AA and DHA incorporation rates and half-lives in rat brain

Measured net brain incorporation rates J_{in}, which were determined following intravenous tracer injection in unanesthetized rats fed standard rat chow (NIH-31), equaled 24 – 48 nmol/g/s × 10^{-4} (0.21–0.42 μmol/g/day) for DHA and 22.0 nmol/g/s × 10^{-4} (0.19 μmol/g/day) for AA [42–45]. As illustrated in Figure 3 (left), the DHA incorporation rate determined this way approximates the DHA rate of loss from rat brain phospholipid, 0.25 μmol/day, which was determined using Eq. 3 from the loss half-life following intracerebral injection of [4,5-^{3}H]DHA [46]. This approximation confirms that J_{in} as calculated following intravenous tracer AA or DHA infusion represents the rate of metabolic loss within brain, and that the circulating precursors LA or α-LNA, respectively, or the esterified PUFAs with circulating lipoproteins, do not contribute significantly to the measured J_{in}.

Half-lives for net DHA or AA loss from rat brain (Eq. 3) are the order of weeks to months (e.g. Figure 3, left side) [35, 46]. They are much longer than the half-lives due to recycling (deacylation-reacylation) (Figure 1) [30, 36], which can be minutes to hours [35, 47]. Recycling is promoted by

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PLA_2-mediated release of AA or DHA from membrane phospholipid, initiated by neurotransmission (see above) [1–3, 22, 37].

PUFA incorporation and consumption rates of the human brain

Recognizing that J_{in} for AA or DHA represents the rate of brain metabolic consumption, we determined J_{in} for both PUFAs in the human brain using PET and the positron emitting tracers, $[1\text{-}^{11}C]$AA and $[1\text{-}^{11}C]$DHA, respectively [48–51] (Umhau et al., unpublished results). Whole-brain J_{in} in healthy adults equaled 17.8 mg/day per 1500 g brain for AA (Figure 4) [49] and 4.6 mg/day per 1500 g brain for DHA (Umhau et al., unpublished results). J_{in} for AA did not decline with age in healthy subjects [49].

Dividing J_{in} for DHA by the estimated human brain DHA content, based on a DHA concentration in gray matter phospholipid of 11.2 μmol/g [Ma et al., unpublished], gives an estimated whole brain DHA concentration of 5.13 g, in agreement with a prior estimate [52], and a DHA half-life of 773 days (2.1 years) by Eq. 3. For AA, whose gray matter concentration is 8.27 μmol/g [Ma et al., unpublished], we calculate a whole brain AA concentration of 3.78 grams and a brain half-life of 147 days.

While a half-life of 2.1 years for DHA seems at first very long, inserting this value in the following equation,

$$c_{brain}(t)=c_{brain}(t=0)e^{-t/t_{1/2}} \tag{Eq. 4}$$

where c_{brain} at the initial time 0 and at time t thereafter are designated, shows that brain DHA would fall by 5% within only 41 days after the disappearance of DHA from plasma. We don't as yet know how sensitive human brain function is to a 5% drop in its DHA content, but if it is, DHA deprivation for only a few months may lead to functional brain changes.

The dietary intakes of n-3 PUFAs for maintaining optimal human brain PUFA metabolism are not agreed on, but now might be estimated by relating intake to PET-determined brain DHA incorporation (consumption) rates. Different committees have recommended eicosapentaenoic acid (EPA, 20:5n-3) + DHA intakes of 0.11–0.16 g/day [53], 0.2 g/day [14], 0.65 g/day [15], and 1.6 g/day [16]. Another committee recommended that adult men and women should consume 1.6 g/day and 1.1 g/day, respectively, of α-LNA, plus an additional 10% of EPA + DHA [53]. Our PET-determined J_{in} for DHA, 4.6 mg/day, equals 2.5–5% of the estimated average daily dietary intake of EPA + DHA in the United States, 100–200 mg/day [13].

Brain and liver conversion of circulating α-LNA to DHA with different diets

Controversy exists about the ability of the brain and liver to convert α-LNA to DHA so as to supplement the brain's DHA, when DHA is absent from the diet or when dietary n-3 PUFAs are low. We evaluated this issue in unanesthetized rats by determining brain consumption rates of DHA under different dietary conditions and by quantifying coefficients and rates of conversion and esterification of circulating α-LNA to DHA in brain and liver [20, 21, 38, 39, 54].

We studied rats that had been fed, for 15 weeks post-weaning (starting at 21 days of age), one of three diets (Table 1, row 1): (1) a high DHA containing diet (DHA 2.3% of total fatty acids, 5.1% α-LNA, 4% fat); (2) a DHA-free diet containing 4.6% α-LNA (of total fatty acids), 10% fat; or (3) a DHA-free diet containing 0.2% α-LNA, 10% fat. We term the latter two diets n-3 PUFA "adequate" and "deficient," respectively, following the convention of Bourre [8]. The rats

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fed the “deficient” compared with “adequate” diet had increased scores on behavioral measures of depression and aggression [55].

As illustrated in Table 1, the unesterified plasma α-LNA concentration in rats fed the n-3 PUFA “adequate” diet was 36% less than in rats fed the DHA-containing diet, but 27 times higher than in rats fed the “deficient” diet (row 2). Unesterified plasma AA did not differ markedly among rats on the three diets, whereas the plasma concentration of the AA elongation product, docosapentaenoic acid (DPAn-6, 22:5n-6), while low in rats fed the high DHA or n-3 PUFA “adequate” diet, rose to 8.7 nmol/ml in rats fed the “deficient” diet (row 3, Table 1).

The DHA concentration in brain phospholipid (Table 1, row 4) was lower in rats fed the “adequate” than high DHA diet, but was reduced by an additional 4.4 μmol/g in rats fed the “deficient” diet. While AA concentrations in brain phospholipid were about the same in rats fed each of the three diets (Table 1, row 5), brain DPAn-6 was elevated by 4.2 μmol/g in rats fed the “deficient” diet, largely compensating for the reduced DHA concentration.

Brain DHA incorporation coefficients k* (Eq. 1) did not vary markedly among the three dietary groups (Table 1, row 6), whereas the rate of DHA incorporation into brain, J_{in}, thus its rate of loss, was reduced in rats fed the deficient diet (Table 1, rows 7 and 8), reflecting the low plasma DHA with this diet (Eq. 2). Reduced values of J_{in} for DHA in rats fed the “deficient” diet corresponded to a 3-fold prolongation of DHA half-life in brain phospholipid (Figure 3, right) [46].

For evaluating brain and liver conversion rates $J_{in,i(\alpha-LNA\rightarrow DHA)}$ of circulating α-LNA to DHA within individual “stable” lipids i (phospholipid, triacylglycerol, cholesteryl ester) [20, 21, 38, 39, 54], we first calculated conversion coefficients $k^*_{i(\alpha-LNA\rightarrow DHA)}$ for each organ following 5 minutes of intravenous infusion of [1-^{14}C]α-LNA. For example, the conversion coefficient for the liver, in units of ml/sec/g liver, equals,

$$k^*_{i(\alpha-LNA\rightarrow DHA)}=\frac{c^*_{liver(DHA),i}(T)}{\int_0^T c^*_{plasma(\alpha-LNA)}\,dt} \quad \text{(Eq. 5)}$$

whereas the conversion rate in units of nmol/sec/g liver equals,

$$J_{in,i(\alpha-LNA\rightarrow DHA)}=k^*_{i(\alpha-LNA-DHA)}\,c_{plasma(\alpha-LNA)} \quad \text{(Eq. 6)}$$

where $c^*_{liver(DHA),i}(T)$ nCi/g is DHA radioactivity in “stable” lipid i, $c^*_{plasma(\alpha-LNA)}$ nCi/ml is plasma radioactivity of unesterified α-LNA, $c_{plasma(\alpha-LNA)}$ nmol/ml is the plasma concentration of unesterified unlabeled α-LNA. Equivalent equations can be written for brain.

The rate of secretion by liver of the DHA assuming that the amount of DHA synthesized from total circulating (unesterified and esterified) α-LNA by the liver, calculated after 5 min of intravenous [1-^{14}C]α-LNA infusion, would eventually be secreted into blood within lipoproteins. This assumption remains to be tested. We calculated the secretion rate by summing equations 5 for i = phospholipid, triacylglycerol and cholesteryl ester, and then dividing by a “dilution” factor $\lambda_{\alpha-LNA-CoA}$ [21, 31, 54]. This factor equals the steady-state ratio of specific activity of liver α-LNA-CoA to specific activity of plasma unesterified α-LNA, during infusion of [1-^{14}C]α-LNA,

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$$ {}_{i}J_{in,i(\alpha-LNA\rightarrow DHA)}/\lambda_{\alpha-LNA-CoA} \quad \text{(Eq. 7)} $$

Taking $\lambda_{\alpha-LNA-CoA}$ into account allows us to estimate the rate of liver DHA secretion from the rate of incorporation only of unesterified circulating α-LNA [31].

We estimated the abilities of the brain and liver to synthesize DHA from circulating α-LNA in unanesthetized rats fed each of the three diets noted in Table 1. As illustrated in row 2 of Table 2, brain conversion coefficients $k^{*}_{i(\alpha-LNA\rightarrow DHA)}$ (Eq. 5) of unesterified plasma α-LNA to DHA into "stable" liver lipids i = phospholipid (PL) and triacylglycerol (TG) did not vary markedly among rats fed the three diets. Thus the net conversion rate was related directly by Eq. 6 to the unesterified plasma concentration of α-LNA (row 2 of Table 1). The calculated net rate of DHA synthesis by the brain (row 4 of Table 2) did not differ between animals on the high DHA diet and the "adequate" diet containing 4.6% α-LNA but no DHA, but was reduced as expected (Eq. 6) in rats fed the "deficient" diet because of the very low plasma α-LNA concentration (row 2, Table 1). In any case, comparing synthesis rates in brain with rates of brain DHA consumption (row 8 of Table 1) shows that the brain's capacity to synthesize DHA is a small fraction of its daily DHA consumption requirement and thus, in the absence of dietary DHA, insufficient to maintain DHA homeostasis.

Comparison of rows 5 and 2 of Table 2 shows that liver conversion coefficients of α-LNA to DHA are many fold their respective brain conversion coefficients. They were increased about 2-times in rats on the "adequate" diet compared with the DHA-containing diet, and a further 7-times in rats fed the "deficient" diet. The increases have since been shown to correspond to increased liver activities of the $\Delta 5$ and $\Delta 6$ desaturases and elongases 2 and 5 that mediate conversion of α-LNA to DHA and of LA to AA [56]. Net liver conversion rates (row 6, table 2) were about the same in rats on the high DHA and n-3 PUFA "adequate" diets, but were reduced in rats fed the "deficient" diet due to the low plasma α-LNA concentration (Eq. 7). The liver's net DHA secretion rate in rats fed the n-3 PUFA "adequate" diet (row 7, Table 2) was many fold greater than the brain's DHA synthesis rate (row 4, Table 2). Furthermore, the liver's secretion rate was about 10-fold the brain's DHA consumption rate (row 8, Table 1), clearly sufficient to supply the brain's DHA.

In summary, in rats fed an n-3 PUFA "adequate" diet containing only 4.6% α-LNA, brain DHA is maintained by the DHA formed and secreted from circulating α-LNA by the liver, as the brain's capacity for DHA synthesis is relatively insignificant. When dietary α-LNA is reduced, the liver increases its coefficients for DHA synthesis by upregulating activities of relevant desaturases and elongases.

Enzymes of the brain AA and DHA cascades in relation to diet

Figure 3 illustrates that the half-life of DHA in brain was prolonged 3-fold in rats fed the n-3 PUFA "deficient" compared with the "adequate" diet [46]. This prolongation corresponds to reduced brain of mRNA, protein and activity levels of the DHA-selective Ca^{2+}-independent phospholipase A_2 (iPLA_2) 25 and of COX-1 [57], as illustrated in Figure 5. Other evidence indicates that these two enzymes are functionally coupled in different tissues [58].

Also illustrated in Figure 5, the 15-week n-3 PUFA "deficient" diet led to increases in brain mRNA, protein and activity levels of AA-selective cPLA_2, secretory sPLA_2 and COX-2 [57], enzymes that are involved directly in brain AA metabolism [26, 58, 59]. These changes, in the context of an increased brain DPAn-6 concentration (Table 1, row 3), imply that the "deficient" diet upregulated brain n-6 PUFA metabolism, and thus that dietary n-3 PUFA supplementation may have an opposite effect.

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Excess AA metabolism can contribute to neuronal damage in experimental ischemia, glutamate excitotoxicity, neuroinflammation, and cerebral trauma [45, 60–64]. This, among other factors, may explain why an n-3 PUFA dietary deficiency might increase brain vulnerability to these insults. In this regard, a low dietary n-3 PUFA content has been suggested to increase brain vulnerability in a number of human diseases, including Alzheimer disease and bipolar disorder, in which neuroinflammation and excitotoxicity play a role [9, 10, 65, 66].

BDNF and CREB

Another way in which dietary n-3 PUFAs may be neuroprotective is by upregulating brain trophic factors. For example, brain derived neurotrophic factor (BDNF) promotes neuronal survival, plasticity, differentiation and growth [67]. Transcription of the BDNF gene is regulated by the cAMP response element-binding protein (CREB), following CREB's phosphorylation by protein kinases including p38 mitogen activated protein (MAP) kinase [68]. In rats fed the n-3 PUFA "deficient" compared with "adequate" diet, brain mRNA and protein levels of BDNF, CREB DNA binding activity, the phosphorylated CREB protein level and p38 MAP kinase activity were reduced significantly (Figure 6) [68]. Another important role of CREB is to modulate memory performance [69].

In summary, rats subjected to our 15-week dietary n-3 PUFA deprivation have a reduced brain DHA concentration and a prolonged DHA half-life, accompanied by reduced activities of presumably DHA-selective $iPLA_2$ and COX-1; an increased brain DPAn-6 concentration accompanied by increased activities of AA-selective $cPLA_2$, $sPLA_2$ and COX-2; and reduced expression of BDNF that corresponds to CREB DNA binding activity and p38 MAP-kinase activity.

3. Conclusions

In this brief review, we have shown how radiotracer methods and kinetic models can be used to determine quantitative aspects of brain and/or liver metabolism of nutritionally essential PUFAs in the intact organism. We have presented experimentally determined regional and global brain AA and DHA consumption rates in humans, and in brain and liver of unanesthetized rats in relation to dietary PUFA composition. In the absence of dietary DHA, we conclude that a normal brain DHA content can be maintained by liver conversion of α-LNA to circulating DHA, provided sufficient α-LNA is in the diet, as the brain's capacity for conversion is quantitatively insignificant. Liver but not brain conversion coefficients are increased by further α-LNA deprivation, in relation to increased expression of liver elongases and desaturases. Brain DHA depletion caused by 15 weeks of dietary n-3 PUFA deprivation in rats is associated with slowed DHA loss from brain and reduced expression of DHA-metabolizing enzymes, tending to conserve brain DHA. At the same time, increased brain expression of AA-metabolizing enzymes and a high DPAn-6 concentration, and reduced brain BDNF, phospho-CREB and p38 MAP kinase activity levels, suggest upregulated brain n-6 PUFA metabolism. Some of these changes are consistent with neuroprotective effects of n-3 PUFAs.

Now that appropriate quantitative techniques are available for studying the relations among brain and liver PUFA metabolism and diet animal and humans, future studies using these techniques might address a number of additional relevant questions: (1) To what extent does the liver convert EPA to DHA under different dietary conditions? (2) What are the effects of graded n-3 PUFA dietary deprivation on the markers and kinetics of brain metabolism and function that we have presented in this paper? (3) What are the effects of dietary n-6 PUFA deprivation on these markers? (4) How do liver conversion rates of α-LNA and EPA to secreted DHA vary with age and liver disease in rats? (5) In humans, how do brain AA and DHA

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consumption rates change with aging or disease, and how might human diets be tailored to maintain normal consumption rates with these variable conditions?

Acknowledgments

This work was supported by the Intramural Program of the National Institute on Aging, National Institutes of Health, Bethesda, Maryland, USA. We thank Dr. Richard Bazinet for his helpful comments

Abbreviations

AA
: arachidonic acid

COX
: cyclooxygenase

DHA
: docosahexaenoic acid

LA
: linoleic acid

PET
: positron emission tomography

PUFA
: polyunsaturated fatty acid

PLA_2
: phospholipase A_2

α-LNA
: α-linolenic acid

BDNF
: brain derived growth factor

CREB
: cAMP response element-binding protein

EPA
: eicosapentaenoic acid

DPA
: docosapentaenoic acid

MAP
: mitogen activated protein

sn
: stereospecifically numbered

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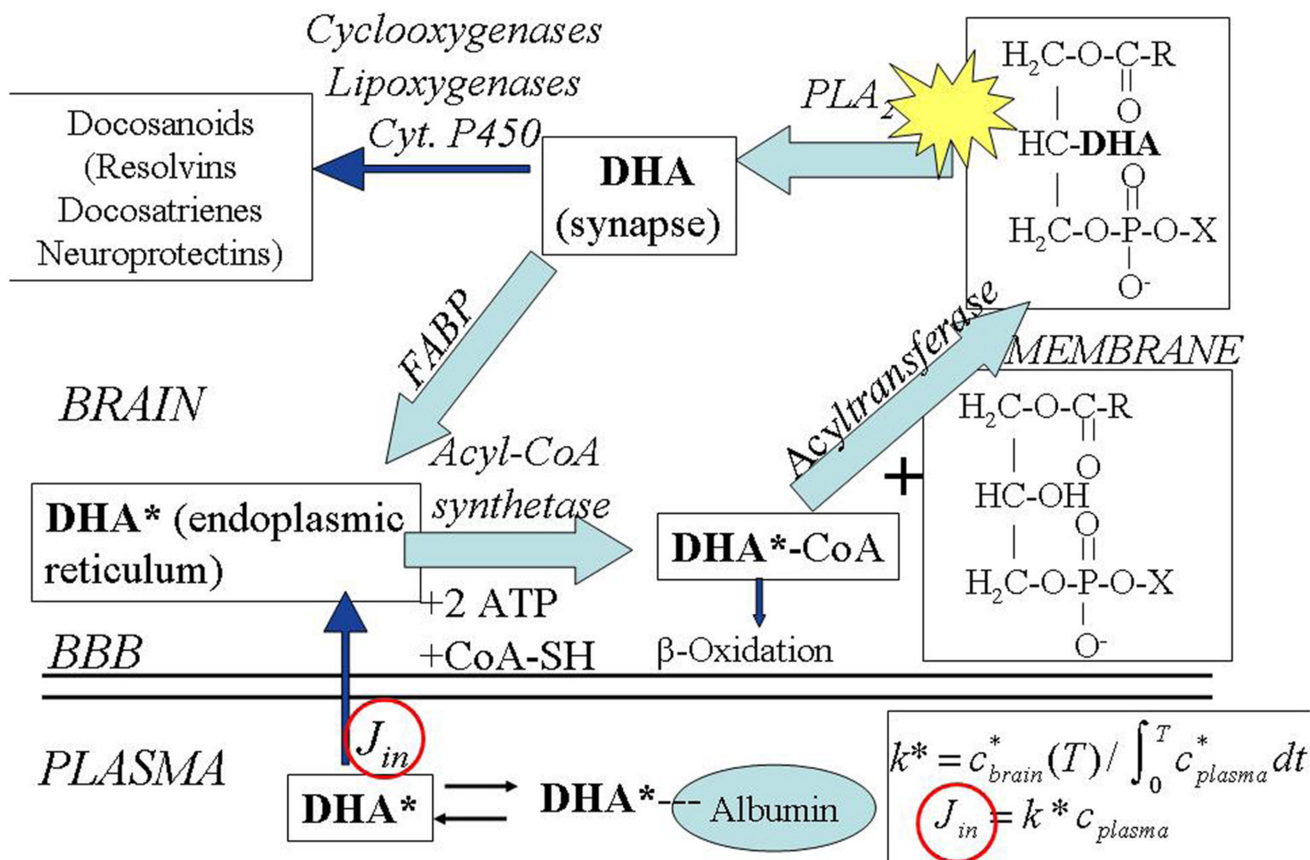

Figure 1. Model of brain docosahexaenoic acid cascade at the synapse

Docosahexaenoic acid (DHA), esterified at the *sn*-2 position of a phospholipid, is liberated by activation (star) of PLA_2 at the synapse, secondary to neuroreceptor activation [1, 37]. A fraction of the unesterified DHA is converted to docosanoids by COX, lipoxygenase or P450 enzymes, whereas the remainder is transported by a fatty acid binding protein (FABP) to the endoplasmic reticulum. From there, DHA is activated to docosahexaenoyl-CoA by an acyl-CoA synthetase with the consumption of two ATPs, then esterified into an available lysophospholipid by an acyltransferase. Unesterified DHA also can be lost by β-oxidation in mitochondria or peroxisomes, or by other pathways (not shown). The endoplasmic reticulum compartment is in very rapid equilibrium with unesterified plasma DHA that has been dissociated from circulating albumin, whereas the synaptic compartment does not exchange with plasma DHA [70]. This allows injecting radiolabeled DHA* intravenously and determining the incorporation rates J_{in} (circled), a critical parameter, of unesterified unlabeled plasma DHA into individual membrane phospholipids, as well as DHA turnover rates and half-lives in those phospholipids. Adapted from [35].

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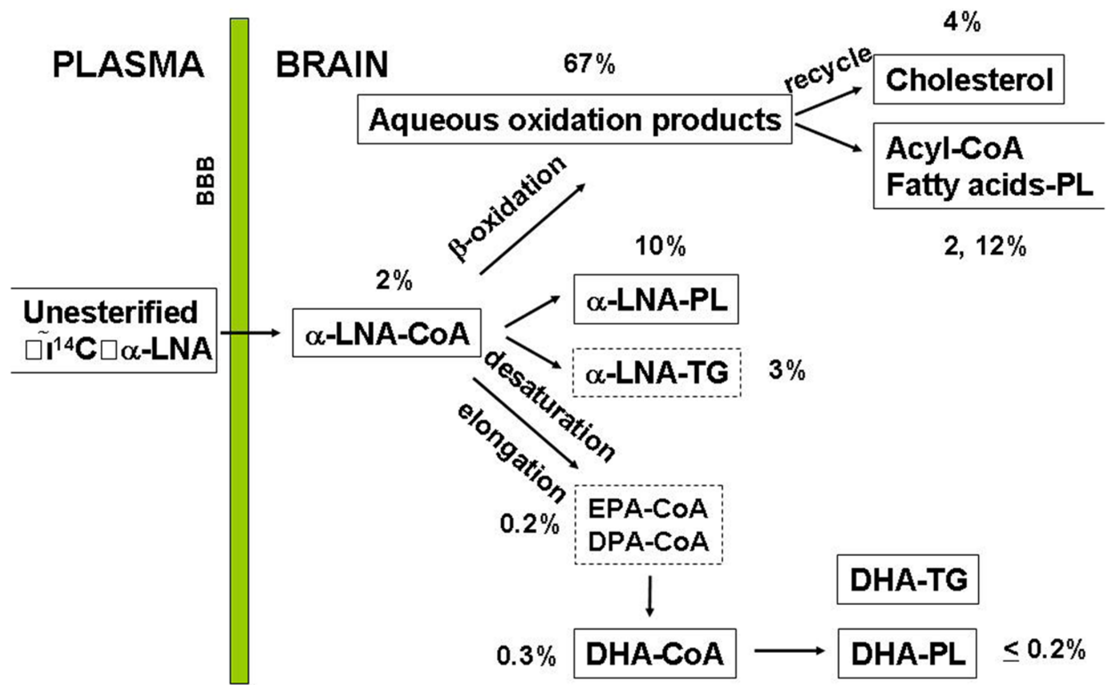

Figure 2. Fractional distribution of [1-^{14}C]α-LNA in different lipid compartments of rat brain, following 5 min of intravenous its intravenous infusion in unanesthetized rats on a high 2.3% DHA containing diet

Less than of the tracer has been elongated to EPA or DHA in the acyl-CoA, phospholipid(PL) or triacylglycerol (TG) pools. From [38].

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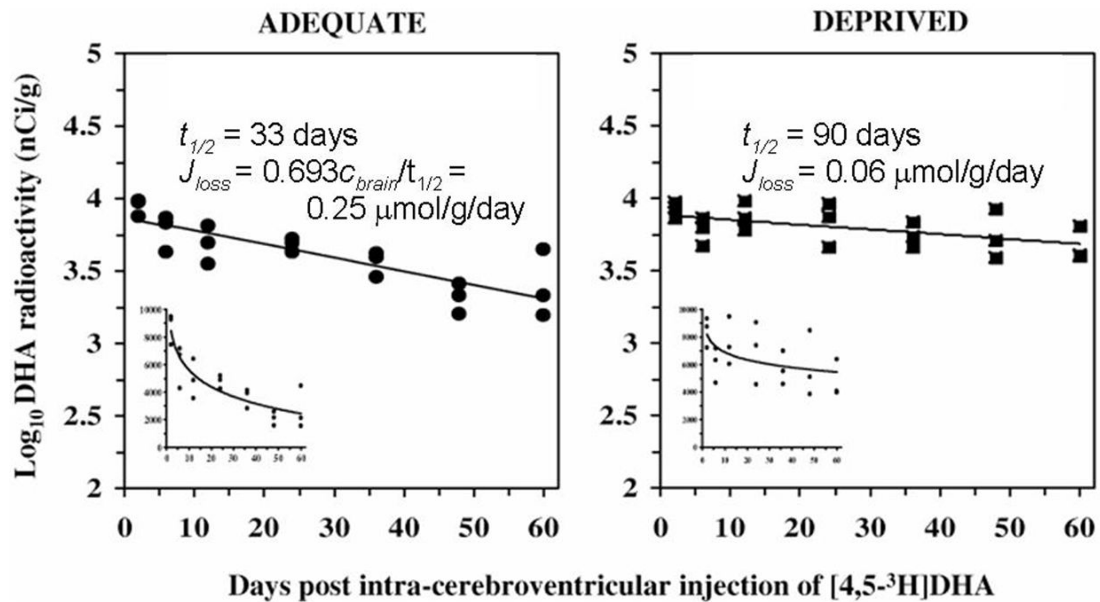

Figure 3. Fifteen weeks of dietary n-3 PUFA deprivation in post-weaning rats prolongs half-life and slows DHA loss in rat brain phospholipid

[4,5-^{3}H]DHA was injected into the brain radioactivity due to it was followed in individual phospholipids for 60 days, from which half-lives $t_{1/2}$ were calculated (Eq. J_{loss} was calculated from half-life as illustrated in figure (Eq. 3). From Demar et al. [46].

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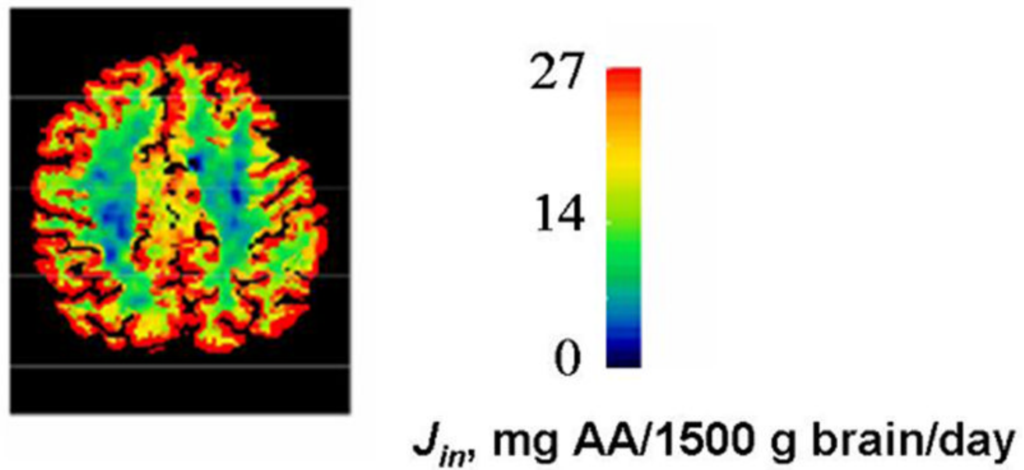

Figure 4. Horizontal section of regional incorporation rates of plasma unesterified arachidonic acid into human brain, after correction for partial voluming

. Rates are given in terms of color-coding. The global rate, obtained by integrating regional rates for whole brain, equaled 17.8 mg/1500 g brain/day. From [49].

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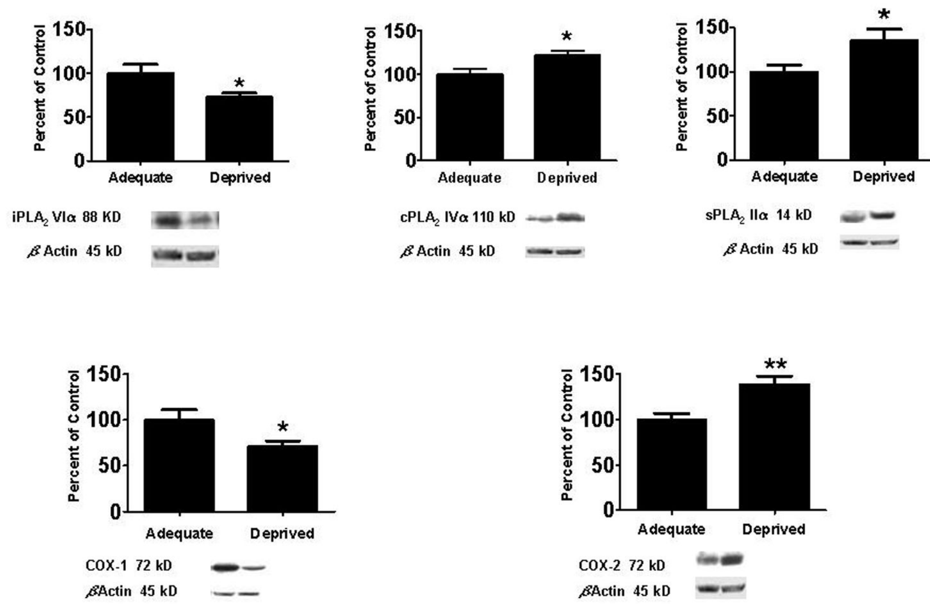

Mean ± SEM (n = 10) *p < 0.05 p < 0.001

Figure 5. Fifteen weeks of n-3 PUFA dietary deprivation, compared with an n-3 PUFA "adequate" diet, decreases rat frontal cortex $iPLA_2$ and COX-1 protein but increases $sPLA_2$, $cPLA_2$ and COX-2 protein

From [57].

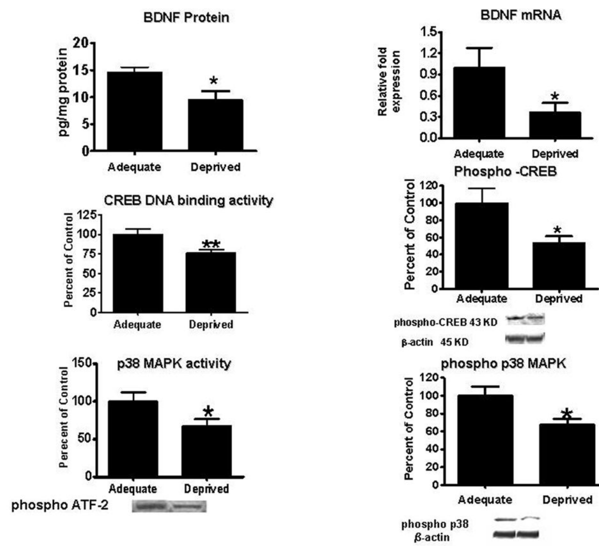

Figure 6. Fifteen weeks of n-3 PUFA dietary deprivation, compared with an n-3 PUFA adequate diet, downregulates rat frontal cortex expression of p38 MAP kinase activity and phospho p38 MAP kinase protein, CREB DNA binding activity and phospho-CREB protein, and BDNF protein and mRNA. From [68]

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Table 1

Plasma and brain parameters in unanesthetized rats fed different diets for 15 weeks

Row 1: dietary composition. Row 2: unesterified plasma concentration of α-LNA and DHA (in brackets). Row 3: unesterified plasma concentrations of AA and DPAn-6 (in brackets); Row 4: Brain phospholipids DHA concentration. Row 5: AA and DPAn-6 (in brackets) concentrations in brain phospholipids. Row 6: DHA incorporation coefficient calculated by Eq. 1. Row 7: brain DHA incorporation rate calculated by Eq. 2. Row 8: whole brain (1.5 g) DHA incorporation (consumption) rate, in units of μmol/day.

			Diet During 15 Weeks Post-weaning		
1	**Parameter**	**Units**	**High DHA diet (5.1% α-LNA, 2.3% DHA, 4% fat)**	**High α-LNA diet (4.6% α-LNA, no DHA, 10% fat)**	**n-3 PUFA inadequate diet (0.2% α-LNA, no DHA, 10% fat)**
2	$\mathbf{c_{plasma}}$**(α-LNA) [**$\mathbf{c_{plasma}}$**(DHA)]**	nmol/ml	$41 \pm 13^{\# a}$ $[26 \pm 12]^{a}$	$27 \pm 6^{\#}$ $[6.5 \pm 2.6]^{b}$	$1.0 \pm 0.45^{*}$ $[0.23 \pm 0.10]^{* b}$
3	$\mathbf{c_{plasma}}$**(AA) [**$\mathbf{c_{plasma}}$**(DPAn-6]**	nmol/ml	22.5 ± 5.6 $[2.3 \pm 1.2]^{c}$	25 ± 4.8 $[\text{ND}]^{b}$	34 ± 5.9 $[8.7 \pm 1.1]^{* b}$
4	**DHA concentration in brain phospholipid,** c_{brain}	μmol/g	17.6 ± 2.8^{a} 13.8 ± 4.9^{c}	12.0 ± 2.4^{d}	$7.6 \pm 1.5^{*d}$
5	**Concentrations of AA and [DPAn-6] in brain phospholipid**	μmol/g	11.1 ± 2.9^{c} $[0.1 \pm 0.04]^{c}$	9.4 ± 1.1^{d} $[0.25 \pm 0.06]^{d}$	9.8 ± 1.5^{d} $[4.4 \pm 1.8]^{* d}$
6	**DHA incorporation coefficients,** k^{*}	$\text{ml/s/g} \times 10^{-4}$	2.2 ± 0.2^{f}	1.99 ± 0.3^{e}	$2.83 \pm 0.6^{* e}$
7	**Rate DHA incorporation,** $J_{in}^{\#}$	$\text{nmol/s/g} \times 10^{-4}$	17.4 ± 2.0^{f}	22.0 ± 5.0^{e}	$0.23 \pm 0.05^{* e}$
8	**Daily rate DHA consumption by whole (1.5 g) brain**	μmol/day	0.23^{f}	0.29^{e}	0.003^{e}

#Mean ± S.D.; AA, arachidonic acid, DHA, docosahexaenoic acid, α-LNA, α-linolenic acid, DPA, docosapentaenoic acid, ND, not detected;

*Differs significantly from mean in high α-LNA (n-3 PUFA adequate) diet rats; #net rate for brain phospholipids

a 38;

b 21;

c 39;

d 46;

e 42;

f 71

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Table 2

Calculated brain and liver conversion parameters in unanesthetized rats fed different diets

Row 1: dietary composition. Row 2: conversion coefficients of plasma α-LNA to DHA in brain, calculated by Eq. 5. Row 3: net conversion rate of α-LNA to DHA, in units of nmol/s/g × 10^{-4}. Row 4: net conversion rate for 1.5 g brain, in units of μmol/day. Row 5: conversion coefficients of plasma α-LNA to DHA in brain, calculated by Eq. 5. Row 6: net liver conversion rate of α-LNA to DHA, in units of nmol/s/g × 10^{-4}, calculated by Eq. 6. Row 7: net DHA secretion rate for 11.5 g liver, in units of μmol/day., calculated by Eq. 7.

			Diet During 15 Weeks Post-weaning		
1	**Parameter**	**Units**	**High DHA diet (5.1% α-LNA, 2.3% DHA, 4% fat)**	**High α-LNA diet (4.6% α-LNA, no DHA, 10% fat)**	**n-3 PUFA inadequate diet (0.2% α-LNA, no DHA, 10% fat)**
			BRAIN		
2	Conversion coefficients brain, $k^{*}_{i(\alpha-LNA \rightarrow DHA)}$ (i = PL, TG)	ml/s/g × 10^{-4}	0.0055, 0.00040	0.0063, 0.00077	0.0051, 0.00089
3	**Net DHA conversion rate per g brain,** $J_{in,i(\alpha-LNA \rightarrow DHA)i}$	nmol/s/g × 10^{-4}	0.24	0.19	0.007
4	**Net daily DHA formation rate from α-LNA by 1.5 g brain**[##]	μmol/day	0.002	0.0016	0.0000006
			LIVER		
5	Conversion coefficients liver, (i = PL, TG), $k^{*}_{i(\alpha-LNA \rightarrow DHA)}$	ml/s/g × 10^{-4}	0.03, 0.1	0.053, 0.219	0.44, 1.45
6	**Net DHA conversion rate per g liver** $J_{in,i(\alpha-LNA \rightarrow DHA)i}$	nmol/s/g × 10^{-4}	6.6	7.45	1.99
7	**Net daily DHA secretion rate, per 11.5 g rat liver**[#]	μmol/day	1.57	2.19	0.82

PL, phospholipid; TG, triacylglycerol;

[#]Calculated by Eq. 7 with $\lambda_{\alpha\text{-LNA-CoA}}$ equal to 0.47, 0.34 and 0.24 for high DHA, 4.6% α-LNA, 0.2% α-LNA diet, respectively, for liver.

From [21, 54, 72]