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Brain arachidonic and docosahexaenoic acid cascades are selectively altered by drugs, diet and disease

Stanley I. Rapoport*

Brain Physiology and Metabolism Section, National Institute on Aging, National Institutes of Health, Building 9, Room 1S128, 9 Memorial Drive, Bethesda, MD 20892, USA

Abstract

Metabolic cascades involving arachidonic acid (AA) and docosahexaenoic acid (DHA) within brain can be independently targeted by drugs, diet and pathological conditions. Thus, AA turnover and brain expression of AA-selective cytosolic phospholipase A₂ (cPLA₂), but not DHA turnover or expression of DHA-selective Ca²⁺-independent iPLA₂, are reduced in rats given agents effective against bipolar disorder mania, whereas experimental excitotoxicity and neuroinflammation selectively increase brain AA metabolism. Furthermore, the brain AA and DHA cascades are altered reciprocally by dietary n-3 polyunsaturated fatty acid (PUFA) deprivation in rats. DHA loss from brain is slowed and iPLA₂ expression is decreased, whereas cPLA₂ and COX-2 are upregulated, as are brain concentrations of AA and its elongation product, docosapentaenoic acid (DPA).

Positron emission tomography (PET) has shown that the normal human brain consumes 17.8 and 4.6 mg/day, respectively, of AA and DHA, and that brain AA consumption is increased in Alzheimer disease patients. In the future, PET could help to determine how human brain AA or DHA consumption is influenced by diet, aging or disease.

Keywords

Phospholipid; Brain; Metabolism; PUFA; Phospholipase A₂ (PLA₂); Arachidonic; Docosahexaenoic; Diet; Lithium; Rat; Human; Bipolar disorder

1. Introduction

Normal brain metabolism, function and structure depend on maintaining homeostatic concentrations of the nutritionally essential polyunsaturated fatty acids (PUFAs), arachidonic acid (AA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3) [1]. Disturbances in these concentrations or in the enzymes that regulate their metabolism have been associated with a number of human diseases, including Alzheimer disease [2] and bipolar disorder [3], and with altered behavior in animals [4].

Recent insights into brain PUFA metabolism have been accomplished with the integrated use of kinetic, analytical and molecular methods, in animals as well as in humans. This

*Tel.: +1301496 1765; fax: +1301402 0074. sir@helix.nih.gov.

review briefly summarizes these methods and some results derived with them. These results suggest that DHA and AA turnover rates within brain phospholipids are regulated by independent sets of selective enzymes. Thus, the brain AA metabolic cascade [5] is downregulated in awake rats treated chronically with mood stabilizers that are effective against the mania of bipolar disorder [6], whereas it is upregulated while the DHA metabolic cascade is downregulated in rats fed, for 15 weeks, a diet low in n-3 PUFAs [7].

2. Kinetic methods

To quantify brain PUFA metabolism *in vivo* in rodents, a loosely restrained unanesthetized rodent is injected intravenously with a radiolabeled PUFA bound to serum albumin. Labeled and unlabeled unesterified PUFA concentrations are quantified in plasma at fixed times until the animal is anesthetized and its brain is removed after being subjected to high-energy microwaving to stop metabolism, or simply is removed and frozen. Lipids are extracted from the microwaved brain and labeled and unlabeled PUFA concentrations are determined in the brain unesterified fatty acid, acyl-CoA and phospholipid pools. The frozen brain is cut into serial coronal slices for quantitative autoradiography, or is used for molecular or enzyme activity analyses. PUFA half-lives due to metabolic loss can be determined by injecting a radiolabeled PUFA intracerebrally, and measuring PUFA-specific activity in individual phospholipids of microwaved brain as a function of time [8]. Positron emission tomography (PET) with intravenously injected positron-emitting [$1\text{-}^{11}\text{C}$]AA or [$1\text{-}^{11}\text{C}$]DHA can be used to measure human brain consumption of AA and DHA [2,9,10].

3. Compartmental representation of brain AA cascade

Fig. 1 illustrates plasma–brain exchange of AA and of its intravenously injected radiolabel (designated as AA*), as well as pathways and compartments of the brain AA metabolic cascade. The cascade is initiated by the activation of a phospholipase A₂ (PLA₂), which releases unesterified AA from the stereospecifically numbered-2 position of synaptic membrane phospholipid [11]. PLA₂ activation is coupled by a G-protein or Ca²⁺ to activation of certain neuroreceptors [12]. A comparable figure can be written for the DHA cascade [13].

After its release by PLA₂, AA is transported to the endoplasmic reticulum and cycled back into phospholipid by the serial actions of acyl-CoA synthetase and acyl transferase. A small fraction however is metabolized to eicosanoids and other products, or undergoes β -oxidation after being transferred to mitochondria from the arachidonoyl-CoA pool by carnitine palmitoyltransferase. Due to the differential affinity of this enzyme for acyl-CoA moieties [14], AA and DHA are largely (90%) reacylated into brain phospholipid and palmitic acid (16:0) is 50% β -oxidized, but linoleic acid (LA, 18: 2n-6) and α -linolenic acid (α -LNA, 18: 3n-3) are almost entirely (about 99%) β -oxidized after entering brain [15,16]. Circulating AA* rapidly reaches equilibrium with brain arachidonoyl-CoA during its intravenous infusion [17].

The coefficient k^* (ml/s/g wet wt brain) of incorporation of unesterified plasma AA into stable brain lipids (mostly phospholipids) is given as

$$k^* = \frac{c_{\text{brain}}^*(T)}{\int_0^T c_{\text{plasma}}^* dt} \quad (1)$$

where $c_{\text{brain}}^*(T)$ (nCi/g) is the labeled esterified brain AA concentration at time T (usually 5 min) after tracer injection, and the denominator (the input function) is integrated plasma radioactivity due to AA*, c_{plasma}^* (nCi/ml), between the start of injection at time $t = 0$ and T .

The rate of incorporation J_{in} (nmol/s/g brain) of unesterified unlabeled plasma AA into brain equals the product of the unesterified *unlabeled* plasma AA concentration c_{plasma} , and the incorporation coefficient k^* ,

$$J_{\text{in}} = k^* c_{\text{plasma}} \quad (2)$$

k^* and J_{in} are unaffected by changes in cerebral blood flow [18], and thus solely reflect brain metabolism. AA and DHA cannot be synthesized *de novo* in brain from 2-carbon fragments [19] or significantly converted from LA (18:2n-6) and α -LNA (18:3n-3), respectively [15,16]. Thus, J_{in} for AA and DHA represents their respective rates of metabolic consumption by brain [20].

AA turnover in brain phospholipids due to deacylation–reacylation (Fig. 1) [21] is given as

$$\text{Turnover due to deacylation – reacylation} = J_{\text{in}} / \lambda c_{\text{brain}} \quad (3)$$

where c_{brain} (nmol/g) equals the unlabeled esterified PUFA concentration in stable brain lipid, and the dilution factor λ equals the steady-state-specific activity of the precursor arachidonoyl-CoA pool divided by plasma AA-specific activity.

4. AA and DHA cascades regulated by separate selective enzymes

AA recycling (Fig. 1), and DHA recycling [13] appear to be independent processes that can be selectively targeted by drugs, diet or disease, as they are regulated by different enzymes. Three major PLA₂ enzymes have been described in mammalian brain: (1) an AA-selective cytosolic phospholipase (cPLA₂) (85 kDa, Type IVA) that requires <1 μM Ca²⁺ for translocation to the membrane plus phosphorylation for activation; (2) an AA-selective secretory PLA₂ (sPLA₂) (14kDa, Type IIA), which is also Ca²⁺ (20 mM) dependent; (3) and a Ca²⁺-independent PLA₂ (iPLA₂) (101 kDa, Type VIA) thought to be selective for DHA [22,23]. cPLA₂ colocalizes and is coupled with cyclooxygenase (COX)-2 at postsynaptic sites [24–26], whereas iPLA₂ is found at these sites and in astrocytes. Acyl-CoA synthetases also can be selective for AA or DHA [27,28].

The brain AA but not the DHA cascade is downregulated in rats chronically given antipsychotic drugs (see below), whereas the AA cascade but not the DHA cascade is upregulated by experimental neuroinflammation or excitotoxicity [29–31]. The two cascades are affected reciprocally (the AA cascade is upregulated while the DHA cascade is diminished) in rats fed an n-3 PUFA deficient diet [7], and in mice in which the gene for α -synuclein, a protein involved in Parkinson disease, has been knocked out [32].

5. Selective targeting of the rat brain AA cascade by mood stabilizers

Bipolar disorder is a life-long neuropsychiatric disease that consists of repeated cycles of manic and depressive episodes (Bipolar I) or of hypomanic and depressive episodes (Bipolar II). It affects 1–2% of the US population, appears initially in young adults, and has a 10–20% lifetime incidence of suicide. Agents called “mood stabilizers” are used to treat the disease [33]. Of these, lithium, carbamazepine [5-carbamoyl-5H-dibenz[b,f]azepine] and valproic acid [2-propylpentanoic acid] are FDA-approved for treating bipolar mania, whereas lamotrigine [6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine] is approved for bipolar depression and rapid cycling. A *common* mechanism that has been suggested to explain the action of *each* of the three antimanic agents is downregulation of the brain AA cascade [6,34,35].

Lithium, valproic acid or carbamazepine, when administered chronically to rats to produce plasma concentrations therapeutically relevant to bipolar disorder, reduced turnover (Eq. (3)) of AA but not of DHA or palmitic acid in brain phospholipids (Table 1). The effect of lithium and carbamazepine corresponded to reduced transcription of AA-selective cPLA₂ and reduced binding of its transcription factor, activator protein-2 (AP-2). iPLA₂ and sPLA₂ were unaffected. Valproate's reduction of AA turnover resulted from its inhibiting an AA-selective microsomal acyl-CoA synthetase, thus acylation of AA to arachidonoyl-CoA (Fig. 1). Each of the three agents reduced the brain COX-2 activity [6], with valproate doing so by downregulating COX-2 transcription and the COX-2 transcription factor, NF- κ B. Lamotrigine did not alter AA turnover but did reduce COX-2 transcription, thus downregulating part of the AA cascade. Topiramate [2,3:4,5-di-*O*-isopropylidene- β -D-fructopyranose sulfamate], an anticonvulsant suggested by initial phase II trials to be effective against bipolar disorder, but later proven ineffective in phase III trials [36], did not significantly change any brain AA or DHA cascade marker. These results suggest that antimanic bipolar drugs downregulate AA turnover and the enzymes that regulate turnover, and that bipolar mania is associated with upregulated brain AA metabolism.

6. Dietary n-3 PUFA deprivation upregulates the arachidonic cascade but downregulates the DHA cascade

The brain AA and DHA cascades can be altered reciprocally by diet or genetic manipulation [32]. With regard to diet, feeding rats an n-3 PUFA deficient diet compared with an adequate diet (containing 0.2% and 4.6% α -LNA, respectively, but no DHA) for 15 weeks post-weaning, increased mRNA and protein levels of AA-selective cPLA₂ and of sPLA₂ and COX-2, but reduced expression of iPLA₂ and COX-1 [7]. These changes were accompanied by increased brain concentrations of esterified AA and its elongation product, docosapentaenoic acid (DPA, 22:5n-6), and by slowed DHA metabolic loss from brain [8,37].

7. Quantifying regional PUFA consumption by the human brain

The rates of incorporation of AA and DHA from plasma into brain, J_{in} (Eq. (2)), equal their respective rates of metabolic consumption by brain (see above). Consumption rates by brain have been estimated with PET in healthy human volunteers [9,10] as 17.8 mg/day for AA and 4.6 mg/day for DHA.

PET also showed that brain AA consumption was higher in patients with Alzheimer disease than in age-matched controls [2]. The elevated consumption is consistent with evidence of inflammation and excitotoxicity in the postmortem brain from Alzheimer patients [38], as it also occurs in animal models of neuroinflammation and excitotoxicity.

8. Discussion

Radiotracer methods and kinetic models have been used to show that AA and DHA turnover rates in rat brain phospholipids are rapid and energy consuming. The recycling (deacylation–reacylation) processes of the two PUFAs appear independent of each other, as they are regulated by independent sets of PLA₂, acyl-CoA synthetase and possibly acyltransferase enzymes, and can be independently targeted by drugs, diet or disease. AA recycling is reduced by chronic administration to rats of agents effective against mania in bipolar disorder, in association with reduced brain expression of AA-selective cPLA₂ or acyl-CoA synthetase, and of COX-2. DHA metabolism and metabolic enzymes are unaffected. In contrast, brain AA but not DHA cascade markers are upregulated in rat models of neuroinflammation and excitotoxicity.

Reciprocal changes in the rodent brain AA and DHA cascades can be produced by dietary n-3 PUFA deprivation or by genetic manipulation. Feeding a low n-3 PUFA diet to rats for 15 weeks reduced brain DHA metabolic loss and expression of DHA-selective iPLA₂ and of COX-1, but increased brain n-6 PUFA (AA plus DPA) concentrations and expression of cPLA₂, sPLA₂ and COX-2. Mice deficient in the α -synuclein gene have downregulated brain AA cascade markers but upregulated DHA cascade markers.

Because AA and DHA cannot be synthesized *de novo* in vertebrate tissue, nor converted from their respective LA and α -LNA precursors, their rates of incorporation from plasma into brain, J_{in} (Eq. (2)), measured following the intravenous injection of their radiolabel, equal their respective rates of metabolic consumption by brain. PET was used to show that brain consumption rates in healthy human volunteers equal 17.8 mg/day for AA, and 4.6 mg/day for DHA. This DHA consumption rate represents 2.5–5% of the estimated average daily dietary intake of eicosapentaenoic acid (EPA, 20:5n-3) and DHA in the United States, 100–200 mg/day [39]. The AA consumption rate is increased in patients with Alzheimer disease, consistent with evidence for neuroinflammation and upregulated AA-selective enzymes in the postmortem Alzheimer brain.

In the future, AA and DHA consumption rates could be measured with PET in relation to human aging, diet and various neuropsychiatric and neurodegenerative diseases. It would be of interest to see if the AA consumption was elevated in the manic phase of bipolar disorder, insofar as effective antimanic drugs downregulate AA metabolism in experimental animals.

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Abbreviations

AA	arachidonic acid
COX	cyclooxygenase
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
DPA	docosapentaenoic acid
LA	linoleic acid
α-LNA	α -linolenic acid
PET	positron emission tomography
PLA₂	phospholipase A ₂
cPLA₂	cytosolic phospholipase A ₂
sPLA₂	secretory PLA ₂
iPLA₂	calcium-independent PLA ₂
PUFA	polyunsaturated fatty acid

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Fig. 1. Model of brain arachidonic acid (AA) cascade. AA at the stereospecifically numbered-2 position of a phospholipid is liberated by activation (star) of phospholipase A₂ (PLA₂) at the synapse. A small fraction of the liberated AA is converted to bioactive eicosanoids. The remainder diffuses to the endoplasmic reticulum while bound to a fatty acid binding protein (FABP), from where it is converted to arachidonoyl-CoA by acyl-CoA synthetase with the consumption of 2 ATPs, then reesterified by an acyltransferase. Unesterified AA in the endoplasmic reticulum exchanges freely and rapidly with unesterified AA in plasma, into which labeled AA (AA^*) has been injected. Equations for calculating kinetic parameters are shown in right lower corner. Adapted from [35].

Table 1

Effective anti-bipolar agents downregulate parts of the rat brain arachidonic acid cascade

Treatment	AA turnover	DHA turnover	cPLA ₂ mRNA, protein, activity ^f	sPLA ₂ mRNA, protein, activity	iPLA ₂ mRNA, protein, activity	AA-selective acyl-CoA synthetase activity	COX-2 protein and/or activity	PGE ₂ ^e
Lithium ^a	↓	Nc	↓	Nc	Nc	Nc	↓	↓
Carbamazepine ^a	↓	Nc	↓	Nc	Nc	Nc	↓	↓
Valproate ^a	↓	Nc	Nc	Nc	Nc	↓	↓ +mRNA ^d	↓
Lamotrigine ^b	Nc	-	Nc	Nc	Nc	-	↓ +mRNA	-
Topiramate ^c	Nc	Nc	Nc	Nc	Nc	-	Nc	Nc

Nc, no change; -, not tested.

^a Preferred for bipolar mania.^b Preferred for bipolar depression.^c Ineffective in phase III trials.^d COX-1 mRNA and TXB₂ also decreased; accompanied by reduced binding NF- κB.^e Formed preferentially *via* COX-2.^f Accompanied by reduced binding of AP-2.