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Reconsidering Dietary Polyunsaturated Fatty Acids in Bipolar Disorder: A Translational Picture

Erika F.H. Saunders[1,2], **Christopher E. Ramsden**[3], **Mostafa S. Sherazy**[1], **Alan J. Gelenberg**[1], **John M. Davis**[4], and **Stanley I. Rapoport**[5]

[1]Department of Psychiatry, Penn State College of Medicine and Penn State Milton S. Hershey Medical Center, Hershey, PA 17033

[2]University of Michigan Department of Psychiatry and Depression Center, Ann Arbor, MI 48109

[3]Section on Nutritional Neurosciences, Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD 20892

[4]Department of Psychiatry, University of Illinois, Chicago, Illinois

[5]Office of Scientific Director, National Institute on Aging, National Institutes of Health, Bethesda, MD 20892

Abstract

Inflammation is an important mediator of pathophysiology in bipolar disorder (BD). The omega (n)-3 and omega (n)-6 polyunsaturated fatty acid (PUFA) metabolic pathways participate in several inflammatory processes, and have been linked through epidemiological and clinical studies to BD and its response to treatment. We review the proposed role of PUFA metabolism in neuroinflammation, modulation of brain PUFA metabolism by antimanic medications in rodent models, and anti-inflammatory pharmacotherapy in BD and in major depressive disorder (MDD). Though the convergence of findings between pre-clinical and post-mortem clinical data is compelling, we investigate why human trials of PUFA as treatment are mixed. We view the biomarker and treatment study findings in light of the evidence for the hypothesis that arachidonic acid (AA) hypermetabolism contributes to BD pathophysiology, and propose that a combined high n-3 plus low n-6 diet should be tested as an adjunct to current medication in future trials.

Keywords

bipolar disorder; inflammation; arachidonic; docosahexaenoic; PUFA; n-3; diet; treatment

Corresponding author: Erika F.H. Saunders, M.D., Department of Psychiatry, Penn State Milton S. Hershey Medical Center, Penn State College of Medicine, 500 University Drive, P.O. Box 850, Mail Code: HO73, Hershey, PA 17033-0850, esaunders@hmc.psu.edu, Tel: (717) 531-4802, Fax: (717) 531-6250.

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Bipolar disorder (BD) affects 1 – 4.4% of the population, and has an episodic, recurrent course which causes significant disability and has a complex, incompletely understood etiology.[1] Effective pharmacotherapies for acute episodes and prevention of relapse include lithium salts, certain antiepileptic agents (e.g. valproic acid, carbamazepine and lamotrigine), and antipsychotic agents.[2]

Though mood-stabilizing medications come from several pharmaceutical classes with differing primary mechanisms of action, downregulation of brain metabolism of arachidonic acid (AA, 20:4n-6), a long chain n-6 polyunsaturated fatty acid (PUFA), has been suggested from pre-clinical studies as one common effect of mood-stabilizing medications.[3–5] Linoleic acid (LA, 18:2n-6) is the dietary-essential shorter-chain n-6 PUFA precursor of AA, which is also consumed in the diet. Alterations of turnover of PUFAs in membrane lipids, including AA, and resultant alterations in cell signaling pathways in brain cell membranes have long been hypothesized to be central to perturbations of neurotransmitter systems in mood disorders.[6,7]

Both studies of biological concentrations of PUFAs, circulating in the plasma or incorporated into red blood cell membranes, and treatment trials using n-3 PUFAs as dietary supplements have had mixed results in BD. While heterogeneity in methods and treatment intervention are confounding factors, one additional reason may be because trials did not also involve alterations in dietary n-6 as well as n-3 PUFA intake. Pre-clinical studies suggest that neurotransmission and other brain functions depend on a balance between n-6 and n-3 PUFAs and their downstream metabolites, such as proinflammatory prostaglandins, lipoxins and thromboxanes, and antiinflammatory resolvins and neuroprotectins, respectively. We present the biological underpinnings of PUFA-related interventions in a physiological, biochemical and molecular context. To do this, we draw upon literature from pre-clinical animal work, post-mortem brain studies and parallel investigations in major depressive disorder (MDD).

We will review evidence for the proposed role of PUFA metabolism in neuroinflammation, modulation of brain PUFA metabolism by antimanic medications in rodent models, and anti-inflammatory pharmacotherapy in BD and in MDD. On the basis of the reviewed evidence, we will propose that dietary manipulation combining high n-3 PUFA with low n-6 PUFA should be tested as an adjunct to traditional mood-stabilizing medications in future clinical trials, rather than using a simple high n-3 PUFA containing diet.

Polyunsaturated fatty acids and Neuroinflammation

The long chain PUFAs, AA (20:4n-6) and DHA (22:6n-3), compose over 90% of PUFAs in the mammalian brain.[8] AA and DHA can be either derived from the diet or be synthesized in the liver from their respective nutritionally-essential shorter-chain PUFAs, LA (18:2n-6) and ALA (18:3n-3). AA, DHA and their metabolites function as intracellular second messengers and as modulators of neuroinflammation, neurotransmission, gene transcription and other important brain process.[6] Proinflammatory cytokines can stimulate release of AA from membrane phospholipids, which then is available for metabolism by cyclooxygenase (COX)-1 or COX-2 to pro-inflammatory prostaglandins (e.g. PGE_2), by lipoxygenases

(LOXs) to cytotoxic leukotrienes, or by cytochrome p450 epoxygenases to cytoprotective epoxyeicosatrienoic acids with the AA metabolic cascade (see Figure 1).[9] PGE_2 affects sleep, and may mediate pain pathways and interleukin-1 induced "sickness behavior," which includes suppressed appetite, social withdrawal, psychomotor retardation and poor concentration, symptoms that overlap with depression.[10–12] Prostaglandins also regulate the hypothalamic pituitary adrenal (HPA) axis by inducing Corticotropin Releasing Hormone (CRH) release.[13,14] Acetylsalicylic acid (aspirin), a COX-1 inhibitor and COX-2 inhibitor and acetylator,[15] reduces the cortisol response,[16] and in a rat neuroinflammation model, chronic low-equivalent dose aspirin reduced brain levels of PGE_2 and 8-isoprostane.[17]

AA is hydrolyzed from membrane phospholipids by cytosolic or secretory phospholipase A_2 (PLA_2). While an early genetic linkage studies of the chromosomal region coding for $sPLA_2$ was promising,[18,19] subsequent studies failed to find significant association between PLA_2 genes and BD.[20–23] Serum PLA_2 levels were reported to be elevated in schizophrenia, BD, MDD, post-traumatic stress disorder and substance abuse.[24] While a subsequent study showed no difference between BD and control in enzyme activity of PLA_2, calcium-independent PLA_2 was elevated in patients with BD and a history of psychosis compared to those without psychosis.[25] A recent study, however, showed lower enzyme activity of 3 PLA_2 species in platelet membranes of drug-naïve BD subjects compared to control.[26] Increased AA metabolism in BD has been suggested by post-mortem brain studies.[27] Compared to control, frontal cortex of BD patients had increased expression of some AA metabolism enzymes, including AA-selective cytosolic $cPLA_2$ IVA, secretory $sPLA_2$ IIA, COX-2 and membrane prostaglandin E synthase (mPGES), while expression others (COX-1 and cytosolic PGES (cPGES)) were reduced, and of others (calcium independent $iPLA_2$ VIA, 5-, 12-, and 15-LOX, thromboxane synthase and cytochrome p450 epoxygenase) were unchanged,[27] suggesting an increase in activity in the AA cascade.[18,21,22] In this regard, a rat model of excitotoxicity using chronic administration of N-methyl-D-aspartate (NMDA), a glutamate receptor agonist, showed increased $cPLA_2$ and increased AA signaling in the frontal cortex.[28,29]

Data from postmortem human brain and animal models are consistent with the proposition that neuroinflammatory processes could contribute to disease progression in BD. Upregulated markers of the pro-inflammatory AA cascade, which activates pathways leading to cell dysfunction and death, have been reported in post-mortem human brain.[27,30,31] Excitotoxic and pro-apoptotic factors were elevated and anti-apoptotic and synaptic markers were decreased in the BD compared to control frontal cortex.[30,32] Studies of peripheral PUFA markers in BD show converging findings that abnormalities in the n-6 and n-3 metabolism pathways are present in BD.[33–40]

Neuroinflammation associated with excitotoxicity and apoptosis in BD may promote future episodes and disease worsening. Although BD is an episodic illness, progressive changes in cognitive function and brain structure occur and correlate with severity and chronicity of illness. Neuroinflammation and excitotoxicity, leading to neuronal apoptosis and synaptic loss, have been hypothesized to underlie progression of BD (reviewed in Berk, et al.[41]). Subtle cognitive changes are reported during and between episodes, and are related to number and amount of time in manic episodes.[42–44] Peripheral markers of inflammation are

elevated in BD.[45,46] Neuroimaging studies also reported brain atrophy and gray matter deficits in emotion regulation circuits linked to length of illness.[47–49] In vivo imaging studies using fMRI have shown hemodynamic changes in the right amygdala and ventromedial prefrontal cortex and left hippocampus in euthymic BD in response to an emotion task, and activation correlated with gene expression in inflammatory pathways.[50] In another study, peripheral markers of inflammation in the kyneurenine pathway were correlated with hippocampal volume.[51] Additionally, a study using positron emission tomography (PET) has shown elevated markers of microglial activation in BD in the hippocampus.[52]

Upregulation of the AA cascade in BD also could modulate signal transduction and interfere with synaptic function,[53] to promote worsening of illness and cognitive changes associated with duration of illness. Changes in the balance between the n-3 and n-6 PUFAs and their bioactive lipid autacoid derivatives (Figure 1) likely influence the inflammatory response.[36]

Anti-manic medications alter AA metabolism

If upregulation of the AA cascade and subsequent neuroinflammation are associated with the pathophysiology and progression of BD, effective treatments for BD might act by downregulating the brain AA cascade.[3–5] Supporting this proposition, chronic administration to rats of a therapeutically relevant dose of lithium reduced AA turnover in brain phospholipids, expression of important AA metabolizing enzymes, and generation of $PGE_{2,}5$ while not affecting DHA and/or palmitic acid (16:0) turnover.[54] Other anti-epileptic drugs with clinically-proven anti-manic efficacy (carbamazepine, valproate, lamotrigine) also downregulated the rat brain AA metabolic cascade,[55–57] while topiramate or gabapentin, anti-epileptic medications that have failed phase 3 trials, did not.[4,58–60] Synthesizing these data has led to the hypothesis that therapeutic downregulation of the AA cascade can be tied specifically to effective treatment of BD. Intervention could involve drugs (see above) as well and changing the PUFA content of the diet (see below).

Pharmacotherapy in BD: anti-inflammatory and n-3 PUFA agents

In addition to the proven effective mood stabilizers, other pharmaceutical agents that interfere with brain AA metabolism would be of interest to investigate clinically in BD. They might include acetylsalicylic acid (aspirin) and other non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., non-selective COX inhibitors), selective COX-2 or COX-1 inhibitors. Stolk, et al. retrospectively used a Netherlands database to investigate effects of some of these agents in subjects on lithium. Long-term low-dose aspirin was associated with reduced risk for worse outcomes, while short-term use of a non-selective NSAID, or of more than one inhibitor, increased risk.[61] Nery, et al. found that celecoxib (Celebrex®), a selective COX-2 inhibitor, for treatment of depression or mixed episode in BD, reduced severity of depression at one week, but did not have a sustained effect in a 6 week double-blind randomized, controlled trial as an adjunct to usual treatment.[62] The effect of anti-inflammatory treatments on mood outcome in BD needs further consideration.

Studies in rodents report differing actions of antidepressants compared with mood stabilizer medication on the brain AA and cytokine-based inflammatory systems. In unanesthetized rats, chronic imipramine and fluoxetine (a selective serotonin reuptake inhibitor, SSRI), antidepressants that can increase risk for switching from depression to mania in BD patients,[63] upregulated brain AA turnover and metabolism (opposite to direction of changes with mood stabilizers), but bupropion, an antidepressant causing lower switch rates, did not.[64,65] These comparisons suggest that increased brain AA metabolism may be associated with the manic phase of BD, and that stimulating AA metabolism may be associated with a switch of depression to mania with certain antidepressants. Indeed, co-administration of lithium, which depresses AA metabolism in rats, is recommended when fluoxetine is administered;[66] it might dampen the untoward AA upregulation of the SSRI. In mice, SSRIs increased inflammatory markers tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma and p11 in the frontal cortex.[67] Because of the complex interactions between AA metabolism and inflammation, the clinical implications of these findings remain to be elucidated. Interestingly, a study of n-3 to prevent IFN-alpha-induced depression in 162 patients treated for hepatitis C showed lower rates of IFN-alpha induced depression in EPA but not DHA treated patients, and both n-3 treatments delayed the onset of depression.[68]

Studies of treatment of BD with supplementation of n-3 preparations, either EPA or DHA or both, have been mixed, and several recent reviews have discussed these studies in detail.[33,69] Briefly, open-label and non-randomized trials have been largely positive,[70–74] while in 5/7 individual randomized clinical trials (RCTs), the intervention group did not separate from placebo for treatment of depression or mania.[75–81] A meta-analysis of RCTs in BD showed a signal for treatment of BD depression, but not mania.[82] Interpretation of the responses seen in RCTs is confounded by factors including differing design of trials, compliance to study drug, composition and dose of supplements, and potential publication bias.

The way forward: Lessons from Migraine

We have described several ways in which altered brain AA metabolism may be important in the pathophysiology and pharmacological or dietary treatment of BD, and have highlighted the mixed results of n-3 PUFA supplementation trials. If the brain PUFA metabolism system is important in BD, what might account for the lack of consistent effects of dietary n-3 PUFA supplementation? One possibility is that n-3 PUFA supplementation without concurrent dietary reduction of n-6 PUFAs may not produce therapeutically-relevant alterations in the interactive brain n-6 and n-3 PUFA pathways.[83,84] In this regard, in the past 100 years, there has been an increase in consumption of the n-6 PUFA precursor LA in the average US diet – the predictable effect of this is increasing tissue concentrations of LA, and decreasing tissue concentrations of n-3 EPA and DHA, and thus an imbalance of n-6 over n-3 PUFAs and their metabolites.[85] Simple addition of an n-3 PUFA supplement without concurrent reduction in dietary n-6 LA may not alter brain PUFA metabolism to the extent required to produce clinically meaningful benefit. To gain some insight into this issue and its relevance to BD, we cite a recent dietary intervention trial in migraine headache.

Migraine headache has a clinical comorbidity with BD of around 30% for both genders when studied together,[86–92] and in a recent study that investigated comorbidity by gender,

39% of women and 16% of men had migraine headache.[93] The pain associated with migraine headache has been hypothesized to be caused by PGE_2,94 and thus related to increased AA metabolism,[95] as well as increased neuroinflammation in general.[96–98] Both BD and migraine headache respond to several of the same medications, including valproic acid[99,100] and lamotrigine,[101] indicating a potential shared pathology.

A recent 12-week randomized clinical trial by Ramsden et al. compared clinical efficacy and biochemical effects of a high n-3 EPA + DHA plus low n-6 LA (H3-L6) diet to effects of only a low n-6 PUFA diet (L6), in 67 patients with chronic headache. Both the H3-L6 and L6 groups experienced statistically significant clinical improvement compared to the pre-intervention run-in phase, but the H3-L6 group experienced a significantly greater reduction in headache hours per day, headache days per month, headache-related quality-of-life and psychological distress.[102] Clinical improvements in the H3-L6 group were accompanied by reductions in erythrocyte LA and AA, as well as bioactive oxidized LA and AA metabolites that have been linked to pain.[103] The H3-L6 intervention also increased n-3 EPA, DHA and the n-3 index, as well as pathway precursors for biosynthesis of anti-inflammatory and pro-resolving EPA and DHA metabolites.[95] Thus, the Ramsden et al. trial suggests that lowering dietary n-6 LA may be a key component to efficacy of n-3 PUFA supplementation in migraine treatment. Based on the clinical and neuroinflammatory links between BD and migraine, concurrent dietary n-6 lowering in BD may also be necessary for effective treatment of BD with n-3 PUFA supplementation.[104]

Summary & Future Directions

An extensive body of human post-mortem and animal studies implicates excessive brain AA metabolism and inadequate DHA metabolism in BD pathogenesis and progression. However, the specific molecular mechanisms linking dysfunctional AA and DHA metabolism to BD are incompletely understood. Future studies should be directed toward identifying specific signaling pathways and lipid mediators linking AA and DHA to BD pathophysiology. This line of inquiry could lead to development of novel, targeted strategies for affecting PUFA metabolism through modulation of dietary AA and DHA intake that can be tested for improvement of mood stabilization in randomized, controlled trials.

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Clinical Points

- Omega-3 and omega-6 fatty acids are important for brain function and are part of inflammatory processes.
- Alteration of fatty acid intake with diet may be an additional way to investigate clinical benefits of changes in the omega-3 and omega-6 pathways.

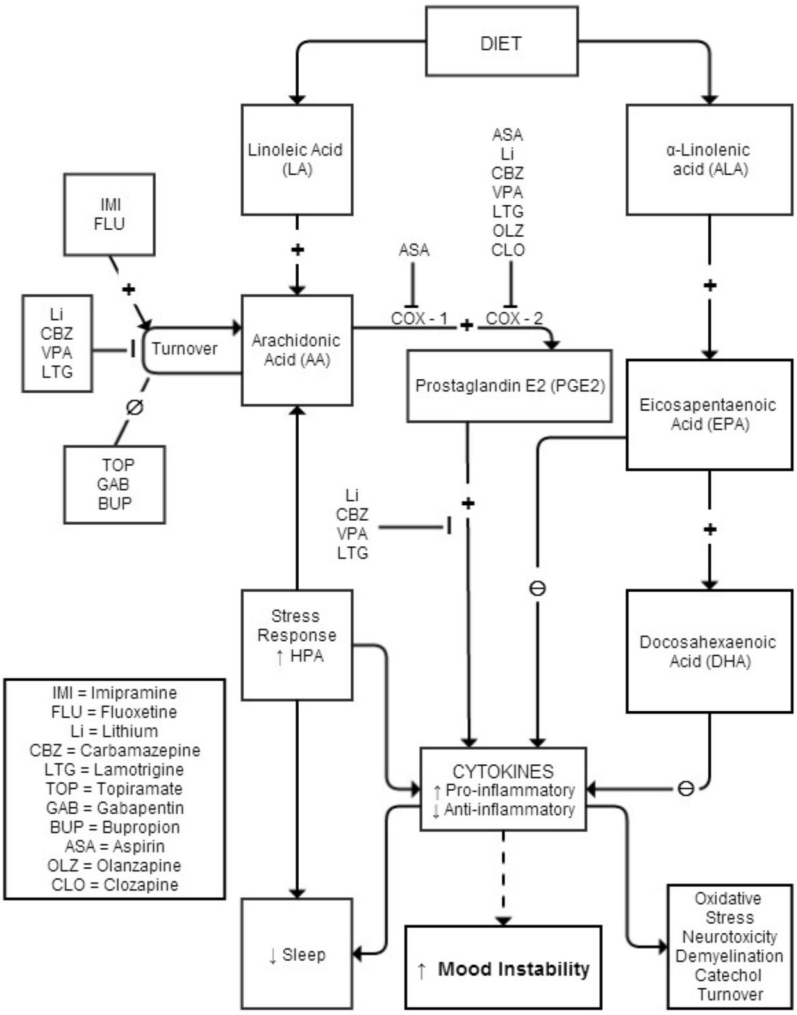

Figure 1.

Impact of psychotropic medication on metabolic pathways of the polyunsaturated fatty acids.