Journal of Psychiatric Research 57 (2014) 58–64

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Dietary intake and plasma metabolomic analysis of polyunsaturated fatty acids in bipolar subjects reveal dysregulation of linoleic acid metabolism

Simon J. Evans [a, *], Rachel N. Ringrose [a], Gloria J. Harrington [a], Peter Mancuso [b], Charles F. Burant [c], Melvin G. McInnis [a]

[a] Department of Psychiatry, University of Michigan, United States
[b] Department of Environment Health Sciences, University of Michigan, United States
[c] Department of Internal Medicine, University of Michigan, United States

ARTICLE INFO

Article history:
Received 30 January 2014
Received in revised form
2 May 2014
Accepted 3 June 2014

Keywords:
Omega-3
Omega-6
Atypical antipsychotics
Eicosadienoic acid
Hydroperoxy octadecadienoic acid

ABSTRACT

Polyunsaturated fatty acids (PUFA) profiles associate with risk for mood disorders. This poses the hypothesis of metabolic differences between patients and unaffected healthy controls that relate to the primary illness or are secondary to medication use or dietary intake. However, dietary manipulation or supplementation studies show equivocal results improving mental health outcomes. This study investigates dietary patterns and metabolic profiles relevant to PUFA metabolism, in bipolar I individuals compared to non-psychiatric controls. We collected seven-day diet records and performed metabolomic analysis of fasted plasma collected immediately after diet recording. Regression analyses adjusted for age, gender and energy intake found that bipolar individuals had significantly lower intake of selenium and PUFAs, including eicosapentaenoic acid (EPA) (n-3), docosahexaenoic acid (DHA) (n-3), arachidonic acid (AA) (n-6) and docosapentaenoic acid (DPA) (n-3/n-6 mix); and significantly increased intake of the saturated fats, eicosanoic and docosanoic acid. Regression analysis of metabolomic data derived from plasma samples, correcting for age, gender, BMI, psychiatric medication use and dietary PUFA intake, revealed that bipolar individuals had reduced 13S-HpODE, a major peroxidation product of the n-6, linoleic acid (LA), reduced eicosadienoic acid (EDA), an elongation product of LA; reduced prostaglandins G2, F2 alpha and E1, synthesized from n-6 PUFA; and reduced EPA. These observations remained significant or near significant after Bonferroni correction and are consistent with metabolic variances between bipolar and control individuals with regard to PUFA metabolism. These findings suggest that specific dietary interventions aimed towards correcting these metabolic disparities may impact health outcomes for individuals with bipolar disorder.

1. Study objectives and background

Bipolar illness affects 2–3% of the US population (Kessler et al., 2005) and carries an average individual economic burden of nearly $12,000 for a single manic episode to nearly $625,000 for chronic unresponsive disease (Begley et al., 2001) and an estimated societal cost of $25–45 billion per year (Begley et al., 2001; Wyatt and Henter, 1995). The lifetime prevalence of suicide attempts in bipolar patients is about 30%, which means that bipolar disorder is a large single risk factor for suicide and suicidal behavior (Novick et al., 2010). Pharmaceutical treatment of bipolar disorder is effective in short-term acute episodic management but often has a limited long-term success and often requires testing several approaches to find a treatment paradigm that approaches an acceptable level of effectiveness. This is likely due to multiple etiologies from the polygenic nature of this disorder and a plethora of environmental contributors.

A substantial environmental contributor may be dietary lipids since epidemiological studies have shown that higher incidences of bipolar and depressive illness associate with lower intake of n-3 polyunsaturated fatty acids (PUFA) (Noaghiul and Hibbeln, 2003). Furthermore, low serum levels of specific n-3 PUFA have been reported in bipolar subjects (Hibbeln et al., 2006) and we have previously reported associations between both plasma n-3 and n-6

* Corresponding author. BSRB 5059, 109 Zina Pitcher Place, Ann Arbor, MI, United States. Tel.: +1 734 936 2036; fax: +1 734 936 2690.
E-mail address: evanssi@umich.edu (S.J. Evans).

http://dx.doi.org/10.1016/j.jpsychires.2014.06.001
0022-3956/

PUFA levels and measures of bipolar disease burden (Evans et al., 2012a, 2012b). Evidence suggests that these observations might be partially explained by genetic variants in specific PUFA-metabolizing enzymes that are differentially expressed in brains of bipolar and depressed subjects (Liu and McNamara, 2011). Also, dietary patterns may be different in bipolar patients, compared to non-psychiatric controls, due to emotional, personal, or socioeconomic reasons (Ellingrod et al., 2011; Jacka et al., 2011; Kilbourne et al., 2007). Thus, there may be gene–diet interactions that are reflected in the tissue levels of PUFAs that vary in bipolar patients relative to controls and effect burden of disease and treatment response.

The n-3 PUFA, alpha-linolenic acid (ALA) and n-6 PUFA, linoleic acid (LA) are essential fatty acids (EFAs) since they cannot be synthesized by mammals and must be obtained in the diet. These two are precursors for the longer chain PUFAs, notably docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) form ALA, and dihomogamma linolenic acid (DGLA) and arachidonic acid (AA) from LA (diagramed in Fig. 1). However, controversy exists around the efficiency of conversion from the EFAs to the longer chain PUFA in humans and the role of dietary intake in regulating the levels of long chain PUFA directly. Plasma levels of EPA and DHA are much more responsive to dietary intake of these n-3 fatty acids and dietary supplementation with ALA does not result in significant accumulation of long chain n-3 fatty acids in plasma (Arterburn et al., 2006). Conversely, AA seems to be tightly regulated and less responsive to dietary intake (Rett and Whelan, 2011). Furthermore, single nucleotide polymorphisms (SNPs) in FADS1 and FADS2 genes, which code for delta-5 and delta-6 desaturase enzymes, respectively, and are involved in the synthesis of long chain PUFA from ALA and LA, partially control levels of AA, DHA and EPA (Tanaka et al., 2009).

Given the metabolic importance of PUFAs, disturbances in this system likely impact several other metabolic pathways as well. For example, a plethora of eicosanoids and related molecules are produced from PUFAs that regulate many physiological functions, a review of which is beyond the scope of this manuscript. Furthermore, medications in the class of mood stabilizers (lithium or valproate) that are prescribed to many bipolar patients to prevent episode recurrence, selectively inhibit AA cleavage from neuronal membranes and concomitant downstream production of inflammatory eicosanoids (Rapoport et al., 2009). This suggests that the biology of PUFA metabolism may be involved in the neurochemistry of bipolar disorder. Bipolar individuals are frequently prescribed medications from the class of atypical antipsychotics for both acute and longer-term management of the illness. These medications have been extensively reported to interfere with various aspects of metabolism, including blood glucose and lipid

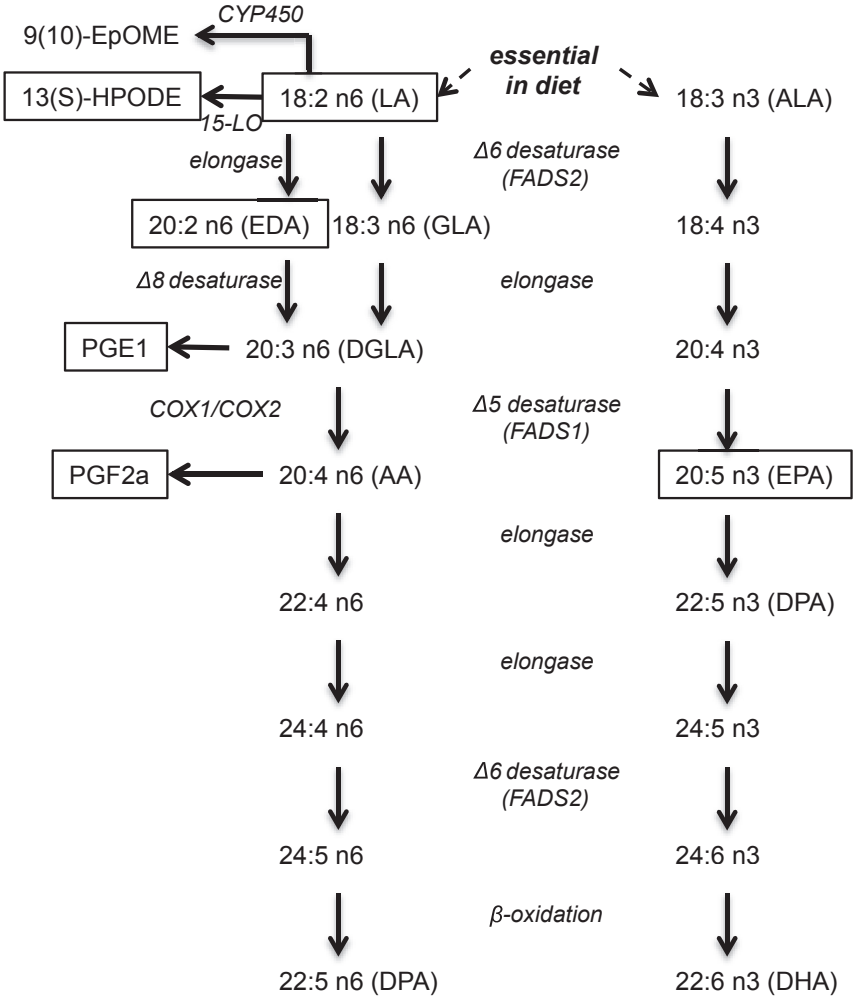

Fig. 1. Schematic representation of PUFA metabolism from the essential fatty acids, LA and ALA. PUFA metabolites found significantly different between bipolar and controls in the current analyses are highlighted with a box, showing the cluster of differences around LA metabolism.