Psychiatry Research ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Psychiatry Research

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

First-episode bipolar disorder is associated with erythrocyte membrane docosahexaenoic acid deficits: Dissociation from clinical response to lithium or quetiapine

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ARTICLE INFO

Article history:
Received 23 April 2015
Received in revised form
19 August 2015
Accepted 22 September 2015

Keywords:
Bipolar disorder
Mania
Lithium
Quetiapine
Arachidonic acid

ABSTRACT

Deficits in long-chain omega-3 (LC$n-3$) fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may be associated with the pathophysiology of bipolar disorder. However, LC$n-3$ fatty acid status at the initial onset of mania and its association with treatment response are not known. Erythrocyte membrane fatty acid composition was determined in first-episode bipolar manic or mixed ($n=40$) and healthy ($n=40$) subjects. Mood symptom ratings were obtained with the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HDRS). Erythrocyte fatty acid composition and clinical ratings were also determined within a sub-group of bipolar subjects following 8-week ($n=19$) or 52-week ($n=11$) open-label treatment with lithium or quetiapine. At baseline bipolar subjects exhibited significantly lower erythrocyte docosahexaenoic acid (DHA, 22:6$n-3$) composition compared with healthy subjects (-23%, $p<0.0001$). EPA (20:5$n-3$) and docosapentanoic acid (22:5$n-3$), and LC$n-6$ fatty acids including arachidonic acid were not different. Following 8- or 52-week treatment with lithium or quetiapine, YMRS and HDRS total scores decreased significantly whereas erythrocyte fatty acids including DHA did not change. These data indicate that selective erythrocyte DHA deficits coincide with the initial onset of manic symptoms, and reductions in mood symptoms following treatment are not mediated by changes in fatty acid status.

1. Introduction

A growing body of evidence suggests that lower habitual dietary intake of long-chain omega-3 (LC$n-3$) fatty acids, including eicosapentaenoic acid (EPA, 20:5$n-3$) and docosahexaenoic acid (DHA, 22:6$n-3$), is associated with the pathophysiology of mood disorders including major depressive disorder (MDD) and bipolar disorder (McNamara, 2015). First, cross-national epidemiological surveys suggest that greater habitual dietary intake of fish/seafood, primary sources of preformed EPA and DHA, is associated with reduced lifetime prevalence rates of MDD (Hibbeln, 1998; Peet, 2004) and bipolar disorder (Noaghiul and Hibbeln, 2003). Second, cross-sectional studies suggest that greater habitual fish or fish oil intake is associated with reduced risk of developing depressive symptoms (Tanskanen et al., 2001; Timonen et al., 2004; Raeder et al., 2007; Lai et al., 2014). Third, meta-analyses of controlled supplementation trials reveal that fish oil is more effective than placebo for reducing depression symptom severity in MDD (Grosso et al., 2014) and bipolar disorder (Sarris et al., 2012). These and other findings suggest that habitual diets containing low amounts of LC$n-3$ fatty acids may increase risk for mood dysregulation.

Erythrocyte (red blood cell) membrane EPA and DHA composition is highly correlated with habitual intake of fish or fish oil (Sands et al., 2005; Flock et al., 2013) and represents a valid biomarker of LC$n-3$ fatty acid status (Harris et al., 2013). Case-control studies have consistently observed reduced erythrocyte EPA and/or DHA levels in adults and adolescents with MDD (Lin et al., 2010; Pottala et al., 2012; McNamara et al., 2014a) and in medicated and

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http://dx.doi.org/10.1016/j.psychres.2015.09.035
0165-1781/

medication-free bipolar subjects (Chiu et al., 2003; Ranjekar et al., 2003; Clayton et al., 2008; McNamara et al., 2010a). Although depression frequently precedes the initial onset of mania (Skjelstad et al., 2010), it is not currently known whether LC$n-3$ fatty acid deficits coincide with the initial onset of mania or are a consequence of chronic illness and/or pharmacological treatments. For example, animal studies suggest that chronic exposure to mood-stabilizer (Rao et al., 2008; McNamara et al., 2008a) or second-generation antipsychotic (McNamara et al., 2009, 2011a) medications alter long-chain fatty acid membrane turnover and composition. Moreover, the relationship between LC$n-3$ fatty acid status and the initial response to pharmacologic treatments is unknown. While prior supplementation studies in medicated bipolar subjects suggest that increasing LC$n-3$ fatty acid status augments therapeutic efficacy (Stoll et al., 1999; Clayton et al., 2009), this relationship has not been evaluated prospectively from a medication-free baseline.

The primary objective of the present study was to compare erythrocyte fatty acid composition in first-episode bipolar manic and healthy comparison subjects. Based on existing evidence, our specific prediction was that first-episode bipolar subjects would exhibit significantly lower erythrocyte EPA and DHA levels compared with healthy subjects. We additionally investigated variables previously found to be associated with EPA and DHA status including gender (Giltay et al., 2004; Bakewell et al., 2006), body mass index (Sands et al., 2005), and cigarette smoking (Leng et al., 1994; Hibbeln et al., 2003). A second objective was to prospectively investigate the effects of 8- or 52-week treatment with either lithium or quetiapine on erythrocyte fatty acid composition and investigate associations with treatment response.

2. Methods

2.1. Participants

Bipolar subjects experiencing a first mixed or manic episode ($n=40$; $n=20$ women, $n=20$ men) were consecutively recruited from the inpatient psychiatric units of the University of Cincinnati Medical Center and Cincinnati Children's Hospital Medical Center. Healthy subjects with no history of a *DSM-IV* Axis I disorder ($n=40$; $n=20$ women, $n=20$ men) were recruited from the greater Cincinnati area. Diagnoses were made with the Structured Clinical Interview for *DSM-IV*, patient version (SCID-I/P) (First et al., 1995). Symptom ratings were obtained with the Young Mania Rating Scale (YMRS) (Young et al., 1978) to assess mania and the 28-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) to assess depression. Both groups were assessed by board-certified psychiatrists with established inter-rater reliabilities (kappa >0.9). Eligible bipolar subjects met *DSM-IV* criteria for type I bipolar disorder, manic or mixed, had a baseline YMRS total score ≥ 20, had ≤ 3 months of lifetime antidepressant medication exposure, had no more than two prior episodes of major depression, and were between 15 and 35 years of age (subjects under 18 years were required to rate at least 4 on the Duke Tanner Pubertal Self Rating scale). Bipolar subjects were excluded from participation if they had a history of mental retardation or an estimated IQ total score of <85 determined by the Wechsler Abbreviated Scale of Intelligence (WASI)(Wechsler, 1999), had a positive urine pregnancy test (in women), or had any substance use disorder within the past three months established with the SCID-I/P in conjunction with the Addiction Severity Index. Cigarette use in the last 30 days was also determined. All subjects provided written informed consent, or if under 18 years of age assent plus consent from a legal guardian. This study was approved by the Institutional Review Boards of University of Cincinnati Medical Center and Cincinnati Children's Hospital Medical Center.

2.2. Treatments

Following baseline evaluations, bipolar subjects were pseudorandomly assigned to open label treatment with either lithium or quetiapine and erythrocyte fatty acid composition and clinical ratings repeated at week 8 or week 52. The quetiapine target dose was 400–600 mg and the lithium target dose was based on achieving serum levels of 0.8–1.2 meq/L achieved in most subjects by doses in the range of 600–1800 mg/day.

2.3. Erythrocyte fatty acid composition

Whole venous blood (4 ml) was collected into EDTA-coated BD Vacutainer tubes, and centrifuged at 4 °C for 20 min (1500x*g*). Plasma and buffy coat were removed and erythrocytes washed 3 times with sterile 0.9% NaCl and stored at −80 °C. Total erythrocyte membrane fatty acid composition was determined with a Shimadzu GC-2010 equipped with an auto-injector (Shimadzu Scientific Instruments Inc., Columbia MD), using the direct saponification method described previously (McNamara et al., 2010a, 2014a). The column was a DB-23 (123–2332): 30 m (length), I.D. (mm) 0.32 wide bore, film thickness of 0.25 μM (J&W Scientific, Folsom CA). The carrier gas was helium with a column flow rate of 2.5 ml/min. Fatty acid identification was determined using retention times of authenticated fatty acid methyl ester standards (Matreya LLC Inc., Pleasant Gap PA). Analysis of fatty acid methyl esters was based on areas calculated with Shimadzu Class VP 4.3 software. The lower limit of detection with a threshold area of 500 and a 1 μl injection volume was approximately 200 ng of an individual fatty acid. Data are expressed as weight percent of total fatty acids (mg fatty acid/100 mg fatty acids) which we have previously found in pilot studies to be highly correlated with fatty acid total mass (μmol/g). Samples were processed by a technician blinded to group assignment.

2.4. Statistical analysis

Group differences in demographic variables were evaluated using unpaired *t*-tests for continuous variables and Chi-square tests for dichotomous variables. Homogeneity of variance was confirmed using Bartlett's test. For the baseline fatty acid analysis we employed Bonferroni correction for multiple comparisons ($\alpha=0.05/17$ comparisons$=0.003$). Categorical assessments were used to determine the percentage of subjects with an 'omega-3 index' (EPA+DHA weight percent of total fatty acids) of ≤ 4.0 percent (Chi-square test). Analysis of interactions with demographic variables was performed with a two-way ANOVA. Baseline-endpoint changes in symptom ratings (YMRS, HDRS) were evaluated with unpaired *t*-tests. Pearson correlation coefficients were used to evaluate relationships among baseline or endpoint erythrocyte fatty acid composition and manic (YMRS) and depression (HDRS) symptom severity scores as well as baseline-endpoint change in symptom ratings. Differences between correlation coefficients were determined using the Fisher r-to-z transformation. For primary outcome measures, effect size was calculated using Cohen's *d*. Using Mplus v6.12 software (Muthen & Muthen, Los Angeles CA), mediation analyses were conducted to estimate: 1) whether selected fatty acid levels mediated variation in YMRS and HDRS scores between groups at baseline, and 2) whether baseline-endpoint changes in YMRS and HDRS scores were mediated by baseline-endpoint changes in fatty acid levels. Bootstrapping was used to estimate confidence intervals on model parameters, including estimates of the indirect (mediated) effects via selected fatty acid levels. All statistical tests were two-tailed

Please cite this article as: McNamara, R.K., et al., First-episode bipolar disorder is associated with erythrocyte membrane docosahexaenoic acid deficits: Dissociation.... Psychiatry Research (2015), http://dx.doi.org/10.1016/j.psychres.2015.09.035