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Plasma free polyunsaturated fatty acid levels are associated with symptom severity in acute mania

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Abstract

Objectives—Nutritionally essential polyunsaturated fatty acids (PUFAs) have been implicated as potentially important factors in mood disorders. For instance, n-3 PUFA supplementation is reported to improve outcomes in major depressive disorder and bipolar disorder. However, the role of PUFAs in acute mania has been minimally investigated. We performed a pilot study to compare plasma levels of free (non-esterified) and esterified PUFAs between patients in an acute manic episode and healthy volunteers, and to explore associations between symptom severity and levels of fatty acids and of the arachidonic acid metabolite, prostaglandin E₂ (PGE₂).

Methods—Patients (n = 10) who were medication-free for at least two weeks and seeking inpatient admission for an acute manic episode were compared with healthy volunteers (n = 10). Symptom severity was assessed at admission and after six weeks of naturalistic treatment. Fasting baseline free and esterified plasma levels of docosahexaenoic acid (DHA, 22:6n-3), eicosapentaenoic acid (EPA, 20:5n-3), arachidonic acid (AA, 20:4n-6) and the AA metabolite PGE₂ were determined, and PGE₂ levels were tested again at six weeks.

Results—No between-group differences were found in levels of individual or total fatty acids, or of PGE₂. Among subjects, manic symptom severity correlated negatively with levels of free AA and free EPA, and positively with the free AA:EPA ratio. PGE₂ levels did not differ between groups or in subjects pre- and post-treatment.

Conclusions—Our preliminary results suggest that, in susceptible persons, low plasma levels of free EPA compared with AA are related to the severity of mania.

Keywords

arachidonic acid; bipolar disorder; mania; polyunsaturated fatty acids; prostaglandins

Nutritionally essential polyunsaturated fatty acids (PUFAs) are increasingly understood to play dynamic roles in the brain, performing direct actions as second messengers (1), modifying receptor expression and binding affinities (2), altering membrane fluidity (3), enhancing neurite outgrowth (4), inhibiting apoptosis in neurons (5), regulating gene expression (6), and producing active metabolites like prostaglandins and leukotrienes (1). Despite their critical functions in the brain, these PUFAs cannot be synthesized *de novo* by mammals, but must be ingested through diet. Deficiency states with regard to essential PUFAs are thus potential etiologic factors in neuro- or psychopathology.

Brain PUFAs fall within two major structural isomer categories, the n-6 and n-3 families (also called 'omega-6' and 'omega-3'), conveying the acyl chain position of the fatty acid's last double bond. Differential levels of n-3 versus n-6 appear to be important in mood disorders. Studies in non-anesthetized rats found that chronic treatment with the mood stabilizers lithium, valproate and carbamazepine decreased arachidonic acid (AA, 20:4n6) turnover in phospholipids and metabolism to prostaglandin E₂ (PGE₂) in the brain (7–10). In humans, subjects with unipolar depression (11–15) and subjects with bipolar depression (BPD) (16) exhibit lower circulating levels of n-3 PUFAs compared with controls, and some studies in depression note higher AA:eicosapentaenoic acid (EPA, 20:5n3) ratios (11,14,17). Increased total n-6 fatty acids are seen in phospholipids of healthy first-degree relatives of patients with bipolar disorders (18). Epidemiologically, high consumption of seafood (a measure of n-3 fatty acid intake) has been associated with lower prevalence rates of BPD (19). Open-label studies of add-on treatment with n-3 PUFAs in BPD have reported reductions in depression (20) and irritability (21). More rigorous, double-blinded, placebo-controlled studies have also found that adjunctive administration of n-3 PUFAs improves outcomes in BPD (22,23) and in unipolar depression (24–26). Moreover, changes in PUFA intake cause measurable alterations in brain functioning in BPD: on magnetic resonance imaging (MRI), whole brain T(2)-relaxation times were decreased in a dose-dependent fashion in subjects after treatment with n-3 PUFAs, compared with untreated subjects (27).

Previous investigation of PUFA levels in acute mania consists of one report (28) of lower AA and docosahexaenoic acid (DHA, 22:6n3) in erythrocyte membranes of subjects compared with healthy volunteers. We sought to investigate group differences in plasma fatty acids and to explore associations between acute manic symptoms with plasma fatty acid and PGE₂ levels.

Methods

Sample

In an Institutional Review Board (IRB)-approved protocol, 10 subjects were enrolled at the time of voluntary inpatient admission to Zucker Hillside Hospital, North Shore Long Island Jewish Medical System. Subjects met DSM-IV criteria for an acute manic episode based on the Structured Clinical Interview-I (SCID-I) (29). This protocol enrolled only patients judged by the treating clinician to have capacity for informed consent. Ten healthy volunteers were recruited through advertisements. Subjects and volunteers underwent physical examination and laboratory screening; exclusions were comorbid DSM-IV Axis I diagnosis, pregnancy, neurologic or medical illness, significant non-steroidal anti-inflammatory use, or current substance use. Dietary and smoking statuses were unknown. Subjects had been off psychotropic medications for $\geq$ two weeks and had no history of substance abuse or dependence unless in full, sustained remission.

Assessments

Illness phase and severity were assessed using the Clinician-Administered Rating Scale for Mania (CARS-M) (30) and the 24-item Hamilton Depression Rating Scale (HDRS) (31). Raters were highly trained, with established interrater reliability.

Biochemistry

Fasting plasma [free (non-esterified) and esterified] fatty acid and PGE₂ levels were measured at study entry, and PGE₂ levels were measured again after six weeks, during which time bipolar subjects received naturalistic treatment. Blood samples for fatty acid determination were obtained in vacutainers containing EDTA and immediately placed on ice. After centrifugation for 10 min at 3000 rpm, the plasma supernatant was transferred to plastic tubes and maintained at -80 °C or on dry ice until processed. Indomethacin was added to blood samples (10 µM final) used for PGE₂ assay to prevent further prostaglandin formation. Biochemical analyses were performed at the Brain Physiology and Metabolism Section, National Institute on Aging, in a blinded manner.

Each plasma sample (0.5 mL) was extracted using the method described by Folch et al. (32). The plasma was mixed with a partition system of 3.0 mL chloroform:methanol (2:1) and extracted with 0.6 mL 0.1 M KCl. Organic extracts were concentrated under N₂ at 45°C, and then suspended in 0.5 mL chloroform. Standards and samples were applied to Silica gel 60 TLC plates and the lipids separated using heptane:diethyl ether:acetic acid (60:40:3) (33). Plates were sprayed with 0.03% TNS in 50 mM Tris buffer (pH 7.4) and lipid bands visualized under UV light. Bands corresponding to non-esterified fatty acid were scraped off and then directly methylated using 1% H₂SO₄ in methanol (v/v) and fatty acid methyl esters (FAME) extracted with heptane (34). Prior to methylation heptadecanoic acid (17:0) was added as an internal standard. For esterified fatty acid determinations, 50 µL plasma extract was concentrated under N₂ at 45°C, then directly methylated as above. FAMES were separated using a gas chromatograph (GC) (Model 6890 N; Agilent Technologies, Palo Alto, CA, USA) with a capillary column (SP 2330, 30 m × 0.32 mm i.d.; Supelco, Bellefonte, PA, USA) and a flame ionization detector (35). Plasma fatty acid concentrations (nmol/mL) were calculated by direct proportional comparison of GC peak areas with that of the added 17:0 internal standard.

For plasma PGE₂ extraction, plasma samples were passed through a C18 reverse phase column (Cayman Chemical, Ann Arbor, MI, USA), which was consecutively rinsed with 5 mL each of ultra-pure water, 15% methanol, and hexane. PGE₂ was eluted with 5 mL ethylacetate into a glass tube. Ethylacetate extract was evaporated under a gentle stream of N₂ and the PGE₂ residue resuspended in the EIA buffer from the PGE₂ high-sensitivity immunoassay kit (R&D Systems, Inc., Minneapolis, MN, USA), which was used to determine PGE₂ concentration.

Statistics

Statistical analyses were performed using SPSS Version 11 for Mac OSX. Subjects and healthy volunteers were compared on the basis of demographic characteristics, individual and total levels of free and esterified DHA, EPA and AA, AA:EPA ratios and PGE₂ levels at the time of admission, using two-tailed independent Student's *t*-tests or Fisher's exact chi-square tests, as appropriate. Within the manic group, we performed Pearson's correlations of CARS-M scores with fatty acid levels, AA:EPA ratios, and PGE₂ levels. Analyses were repeated using individual free fatty acids as a percent of total free fatty acids, using log transformations due to non-normal distribution. We also compared PGE₂ levels at the time of admission and six weeks after treatment, using a paired Student's *t*-test. As within-group analyses were exploratory, we made no corrections for multiple comparisons.

Results

The following demographic characteristics of the bipolar subject and healthy volunteer groups were observed, respectively: mean age (33.1 ± 12.4 versus 37.8 ± 14.6 years); educational level (13.6 ± 2.1 versus 14.4 ± 1.5 years of schooling); sex [five (50%) male in each group]; marital status [five (50%) versus six (60%) married]; and race [nine (90%) versus six (60%) white]. The main clinical characteristics of interest were assessed with mania and depression rating scales. CARS-M scores ranged from 16 to 47; mean scores were 29.2 ± 9.6 at study entry and 7.3 ± 5.6 after treatment. We did not exclude subjects with comorbid depressive symptoms. HDRS (24-item) scores at study entry ranged from 4 to 22, with a median of 10.5.

No difference was found between groups in initial levels of fatty acids, PGE₂ or the AA:EPA ratio (Table 1), nor was any difference seen pre- and post-treatment in PGE₂ levels among bipolar subjects (pre-treatment 2160.4 ± 1869 pg/mL versus post-treatment 2643.8 ± 1946.3 pg/mL). A post hoc analysis found that the power to discern between group differences for this sample size was $\leq 50\%$.

Among bipolar subjects, severity of manic symptoms negatively correlated with absolute levels of free AA (Pearson's $r = -0.801$, $p = 0.009$) and EPA ($r = -0.678$, $p = 0.045$) (Fig. 1), but not with the respective esterified forms. Correlations remained significant when free AA or EPA as a percent of total free fatty acids were used, after log transformation to correct for non-normal distribution (data not shown). The associations between low fatty acid concentrations and severity of manic symptoms persisted after adjustment for HDRS scores. HDRS scores did not correlate with any fatty acid, and there was no interaction between CARS-M and HDRS scores. A positive correlation was seen between symptom severity and the AA:EPA ratio (Pearson's $r = 0.675$, $p = 0.046$; Fig. 1). PGE₂ levels did not correlate with free or esterified AA (data not shown).

Discussion

Clinical findings

Recruitment for this study was challenging, as manic symptoms may interfere with concentration and judgment. Despite this, we enrolled 10 subjects who were clearly experiencing moderate to severe mania. However, it is likely that our sample did not include the most severely ill segment of this population. Our expectation was that a larger number of patients would be screened, based on clinical lore that manic relapse typically occurs in the context of medication non-compliance. However, in this 208-bed psychiatric hospital, which admits about 140 acutely manic patients/year, we found that, on average, less than one patient/month presented to the daytime emergency service having stopped medications for $\geq$ two weeks without substance abuse/dependence. Thus, medication non-adherence may be overrated as a cause of manic relapse, or relapse in the absence of medications may occur more rapidly than over two weeks or may most frequently occur in the context of substance use (including antidepressants).

Biochemical findings

Chiu et al. (28) reported lower levels of erythrocyte membrane DHA and AA in manic subjects compared with healthy volunteers. We were unable to detect differences in plasma PUFA or PGE₂ levels between groups in our small sample but did find that within the bipolar group lower levels of free AA and EPA were associated with more intense manic symptoms (Fig. 1A,B).

Our data do not allow determination of whether low PUFA levels may contribute to or result from BPD. Others (22), however, have found that PUFA supplementation prolongs the time

to relapse in BPD, suggesting that lower PUFA levels could be a factor in the development of affective illness episodes. An overlap in fatty acid levels between groups could mean that a culturally normative fatty acid intake is not adequate for health in BPD.

PUFA levels in both erythrocytes (34) and plasma (36) have been shown to reasonably reflect brain PUFA changes. Previous research on PUFA levels in mood disorders has utilized both erythrocyte (12,13,17,28) and plasma (11,14) levels. This study utilized plasma levels, which we reasoned may be a better indicator of recent changes in fatty acid consumption, in case the onset of mania is related to acute dietary fluctuations. Furthermore, absolute levels of PUFAs are more reproducibly obtained from plasma and more reliably quantifiable (per volume of plasma), compared with erythrocytes, where data are usually reported as percentages of total fatty acids and volume is more ambiguous (per weight or volume of packed red blood cells).

We found that free but not esterified plasma fatty acid levels correlated with manic symptoms. One interpretation is that plasma free fatty acids may more accurately reflect the brain fatty acid milieu; this would be consistent with some studies in rat brain, which found that it is primarily the non-esterified (free) fatty acids that cross the blood–brain barrier (35,37–39), although mechanisms for the transfer of esterified forms of fatty acids have also been demonstrated (40–42).

Among bipolar subjects, not only lower levels of free AA and EPA, but also lower levels of free EPA *relative to* free AA correlated with manic symptom severity (Fig. 1C). That is, although both AA and EPA were lower as symptom severity increased, EPA (in the range of 20-fold) was lowered proportionately more than AA (3-fold); thus variability in the ratio was mostly accounted for by changes in EPA levels. A larger AA:EPA ratio has not been observed previously in mania (28), but has been reported in depressed subjects compared with healthy volunteers (11,14,17). If our findings are replicated in future studies, it would indicate that a brain AA > EPA (or n-6 > n-3 PUFA) imbalance may be a non-specific contributor to illness in either mood direction. Hypothetically, either reducing AA or increasing EPA could normalize the AA:EPA ratio. However, it has been suggested that n-3 supplementation may be more effective in depression than in mania (43,44): for example, in a preliminary, placebo-controlled, double-blinded study of n-3 augmentation in BPD (22), depressive but not manic symptoms were significantly improved. Further, preclinical studies in rats (7–10) found that a variety of mood stabilizers of differing chemical structures serve to downregulate AA turnover. It is possible that there are differentially specific therapeutic effects of AA reduction in mania and EPA supplementation in depression.

Our study is limited by its small sample size and the lack of information about dietary and smoking history. Lower dietary intake of n-3 relative to n-6 fatty acids has been found to be associated with increased prevalence of depression (45,46) and aggression (47), while high dietary intake of n-3 has been related to decreased hostility (48), decreased symptoms of post-partum depression (49) and lower prevalence rates of BPD (19). It is not known whether the effects of PUFAs in mood disorders may also be related to anomalies of fatty acid metabolic processes.

These preliminary findings imply that optimizing the ratio of n-6 to n-3 PUFAs in the plasma, through dietary or drug interventions, may prove to be a favorable adjunct treatment for preventing or diminishing the manic phase in BPD. More information is needed about the potential role of fatty acids in the etiology and prevention of acute manic episodes.

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Fig. 1.

Correlations within the bipolar subject group between severity of acute manic symptoms and fasting levels of plasma free fatty acids at the time of study enrollment. (A) Arachidonic acid (Pearson's $r = -0.801$, $p = 0.009$). (B) Eicosapentaenoic acid (Pearson's $r = -0.678$, $p = 0.045$). (C) Ratio of arachidonic acid to eicosapentaenoic acid (Pearson's $r = 0.675$, $p = 0.046$). One outlier was removed from all analyses. CARS-M = Clinician-Administered Rating Scale for Mania.

Table 1

Plasma levels of fatty acids and prostaglandin E₂ in subjects with acute mania versus healthy volunteers

Fatty acids mean (SD)	Subjects in manic episode						Healthy volunteers					
	Free			Esterified			Free			Esterified		
	n	Absolute value nmol/ mL	% of total free FA	n	Absolute value nmol/ mL	% of total free FA	n	Absolute value nmol/ mL	% of total free FA	n	Absolute value nmol/ mL	% of total free FA
Arachidonic acid (AA 20:4n-6)	9	3.35 (1.92)	1.5 (0.92)	9	1,482.6 (838.7)	9.8 (1.9)	9	2.78 (1.63)	0.94 (0.45)	10	1,153.6 (527.0)	8.4 (4.2)
Docosahexaenoic acid (DHA 22:6n-3)	9	1.62 (1.33)	0.74 (0.56)	8	257.5 (141.8)	2.2 (0.8)	8	1.48 (0.76)	0.45 (0.18)	10	206.8 (106.9)	1.5 (0.8)
Eicosapentaenoic acid (EPA 20:5n-3)	9	0.37 (0.35)	0.13 (0.07)	9	97.3 (87.6)	0.54 (0.18)	8	0.36 (0.19)	0.12 (0.08)	9	84.0 (59.2)	0.43 (0.2)
Total fatty acids	9	278.9 (163.8)	100	9	16,747.6 (12,385.6)	100	9	286.2 (143.8)	100	10	18,217.9 (15,255.8)	100
AA to EPA ratio	9	14.98 (9.09)		9	20.02 (8.07)		8	9.66 (4.21)		9	19.03 (9.54)	
		n	Mean (SD) pg/mL				Mean (SD) pg/mL					
Prostaglandin E ₂ (time 0)		8	2,160.4 (1,869.4)				2,643.8 (1,946.3)					

No significant differences between subjects and healthy volunteers were found using two-tailed Student's *t*-tests. One outlier was removed from the bipolar subject group. FA = fatty acids.