

## Polyunsaturated fatty acid deficit in patients with bipolar mania

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### Abstract

The aim of this study is to test the hypothesis that there is a depletion of polyunsaturated fatty acids of erythrocyte membranes in patients with bipolar disorder and to connect the previous therapeutic and psychoimmunological findings. Fatty acid compositions of erythrocyte membranes in 20 bipolar manic patients and 20 healthy controls were analyzed by thin-layer chromatography and gas chromatography. The major finding was significantly reduced arachidonic acid (20:4n-6) and docosahexaenoic acid (22:6n-3) compositions in bipolar patients as compared to normal controls with *P* values of 0.000 and 0.002, respectively. There were no differences in total omega-3 and omega-6 polyunsaturated fatty acids. This abnormality may be related to the mechanisms of action of mood stabilizers and the previous findings on the abnormal psychoimmunology of patients with bipolar disorder. Larger sample sizes of medicated patients or drug-free manic, well-controlled designs on the diet and smoking, and fatty acid composition measurements during full remission after the index episode are warranted in future studies.

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### 1. Introduction

Several investigators (Stoll and Severus, 1996; Manji and Lenox, 1998) strongly suggested that the mechanism of action of mood stabilizers is involved in postsynaptic signal transduction processes. Two mood stabilizers (lithium and valproate) appear to treat the same symptoms of patients with bipolar disorder, through different effects on signal transduction in the brain. Recently, Chang et al. (2001) found that lithium and valproic acid have a common action in reducing turnover of arachidonic acid (AA), the major omega-6 polyunsaturated fatty acids

(PUFA) in rat brain. Furthermore, a 4-month double-blind, placebo-controlled study, comparing omega-3 PUFAs vs. placebo, in addition to usual treatment, suggested that omega-3 PUFAs may exhibit mood-stabilizing properties in bipolar disorder (Stoll et al., 1999). Thus, PUFAs, as well as lithium and antimanic anticonvulsants, seem to play an important role in the mechanism of mood stabilization by targeting parts of the "arachidonic acid cascade", which may be functionally hyperactive in mania (Rapoport and Bosetti, 2002).

It has been hypothesized that abnormalities in fatty acid composition may play a role in psychiatric disorders (Horrobin and Bennett, 1999). Maes et al. (1996, 1999) reported that patients with major depression had a significantly elevated ratio of ecosapentaenoic acid (EPA; 20:5n-3)/docosahexaenoic acid (DHA; 22:6n-3), lower level of EPA and total n-3 PUFAs, in both serum chole-

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teryl esters and phospholipids when compared to patients with minor depression and normal controls. Similar findings were revealed in terms of fatty acid compositions of the erythrocyte membrane (Adams et al., 1996; Edwards et al., 1998; Peet et al., 1998). Generally, PUFAs are classified mainly into omega-3 (or n-3) and omega-6 (or n-6) groups. Cerebral cell membranes are composed of certain PUFAs, which cannot be synthesized and must therefore be obtained from the diet. The abnormalities in PUFA composition in cell membranes can alter membrane microstructure, resulting in abnormal signal transduction and immunological regulation. In general, the omega-6 fatty acid, AA is proinflammatory and associated with up-regulation of release of various cytokines. In contrast, the omega-3 fatty acids, EPA and DHA, are anti-inflammatory (Horrobin and Bennett, 1999). Interestingly, patients with bipolar disorder have also been reported to have altered immune functions (Kronfol and House, 1988), including leukocytosis (Kronfol et al., 1988), higher prevalence of thyroid autoantibodies (Lazarus et al., 1986), high rate of immune-related diseases (Tsai et al., 1997), and abnormalities in cytokine levels (Maes et al., 1995; Su et al., 2002; Tsai et al., 1999, 2001). Thus, PUFAs also seem to play an important role in the abnormality of psychoimmunology of patients with bipolar disorder.

Despite this evidence from animal studies, psychoneuroimmunology studies, and clinical trials, well-controlled studies on PUFA levels in bipolar manic patients are still sparse. Mahadik et al. (1996) reported the only study that compared PUFA compositions of cultured skin fibroblasts of 12 schizophrenic patients to those of six bipolar patients and eight normal control subjects. They found that there was no difference between bipolar patients and normal subjects. However, their results are difficult to interpret due to various limitations. (1) The sample size is small ( $n=6$ ) and the aim of their study is to examine the abnormalities of fatty acids in schizophrenic rather than bipolar patients. (2) The clinical status, such as durations of the illness, mood state (mania, depression or mixed), the severity of the symptoms, in these bipolar patients was not well-defined or controlled. (3) No information was given regarding to the use of the mood stabilizing drugs and the antipsychotic drugs, which were also found to influence the PUFA levels (Horrobin et al., 1997). (4) The PUFA level from fibroblasts (instead of erythrocyte) has not been confirmed to reflect that in the brain (Neuringer et al., 1984; Makrides et al., 1994).

To address these issues, we conducted a study on erythrocyte PUFAs in acute manic patients compared with matched normal controls.

## 2. Subjects and methods

Forty subjects (20 healthy volunteers and 20 patients with bipolar disorder) were recruited in this study. All of them were free of any medical illness, including immune

and endocrine disorders. Their ages were ranged between 18 and 65 years. The patients were admitted to the psychiatric ward at Taipei City Psychiatric Center, Taiwan. All participants were Hans in ethnicity and other minorities were excluded from this study. Excluded were also those who were on a low fat diet or vegetarians. The healthy controls were free from having any positive family history of mental disorder and taking any psychotropic agents.

Enrolled patients met DSM-IV (American Psychiatric Association, 1994) criteria for bipolar I disorder, most recent episode manic. The bipolar patients who had mixed episode of mood symptoms or other comorbid Axis I psychiatric disorders (i.e., psychiatric disorders due to a general medical condition or induced by substance uses) were excluded. During the index hospitalization, all patient subjects continued to receive existing mood stabilizers, benzodiazepine and antipsychotic drugs. After having signed written informed consent, the patients and controls were sampled for venous blood between 08:30 and 09:30 after overnight fasting.

Blood samples were analyzed for individual fatty acids with gas chromatography of methyl esters. Individual fatty acids were identified by comparison of gas chromatograms (Lipid Standards, FAMES, Sigma, St. Louis, MO, USA). The detailed step-by-step procedures are described elsewhere (Edwards et al., 1998; Maes et al., 1999). Briefly, 0.5 g of centrifuged, washed red blood cells was placed into 16×150 mm test tubes with Teflon-lined screw caps, followed by addition of 2 ml methanol–benzene solution (1:1, v/v). Samples were vortexed at low speed while slowly adding 200  $\mu$ l of acetyl chloride. Then, they were gassed with N<sub>2</sub>, capped tightly and heated at 100 °C for 30 min. After samples were cooled to room temperature, 5 ml of 6% K<sub>2</sub>CO<sub>3</sub> was added and the sample vortexed for 30 s. Thereafter, samples were centrifuged 10 min at 1500×g, and the benzene layer (upper layer) was taken and washed three times (10 min at 1500×g) with distilled, deionized water. The upper layer was then removed and placed in injection vials for analysis. Heptadecaenoic acid was added as the internal standard. Fatty acid methyl esters (FAMES) were analyzed by capillary gas chromatography (Hewlett-Packard 5890 II Plus, Hewlett-Packard, Palo Alto, CA, USA) equipped with a 25 m×0.32 mm I.D. capillary column (Hewlett-Packard FFAP, 0.25  $\mu$ m film thickness, Hewlett-Packard) and flame ionization detection. The injector and detector temperatures were 230 and 250 °C, respectively, and the split ratio was 100:1. Initially, the oven temperature was set at 160 °C for 4 min, and was then increased at 2.5 °C/min to 225 °C and held for 20 min. Peaks were integrated by a programmable integrator (Hewlett-Packard 3395, Hewlett-Packard). Fatty acid profiles were identified by comparing the retention times with those of appropriate standard FAMES. Laboratory measures were conducted on coded samples by workers who were blind to the information whether samples were from bipolar subjects or controls.

Data were analyzed by using the Statistical Package for

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