Essential polyunsaturated fatty acids and social cognition in schizophrenia

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Abstract

Abnormal metabolism of essential polyunsaturated fatty acids (EPUFAs), a component of phospholipids in neural membranes, has been suggested to be related to the pathophysiology of schizophrenia. The purpose of this study was to examine the relationship between EPUFA concentrations in erythrocyte membranes, a peripheral measure of phospholipid composition in the brain, and clinical variables, such as cognitive performance relevant to social functions, in patients with schizophrenia. Erythrocyte membrane levels of EPUFAs, saturated fatty acids, and monounsaturated acids were measured in 25 patients with schizophrenia and 32 age- and gender-matched 32 normal volunteers. The script tasks, a measure of social cognition, and the Brief Psychiatric Rating Scale were administered to the patients. The levels of EPUFAs, but not those of saturated or monosaturated fatty acids, were significantly lower in patients than in normal controls. The degree of a decrease in EPUFA levels was positively correlated with severity of positive symptoms and impairment of frequency judgment performance on the script tasks, while no such correlations were found with negative symptoms, attention as measured by the Wechsler Adult Intelligence Scale-Revised-Digit Span, or verbal memory as measured by the Auditory Verbal Learning Test. These results provide the first suggestion for a contribution of decreased levels of EPUFAs to impaired social cognition, as represented by event schema, in patients with schizophrenia.
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1. Introduction

Disturbances of cognitive functions, such as memory, executive function, verbal fluency and attention, are characteristic of most patients with schizophrenia or related disorders (Saykin et al., 1991; Sumiyoshi et al., 2001a,b, 2004, 2005; Matsui et al., 2004; Keefe et al., 2005). Cognitive performance has been shown to have a significant influence on important outcome measures, including work and social function. Among tests of cognitive performance, script tasks have been developed as a measure of social cognition (Chan et al., 1999; Matsui et al., 2006). These tasks are used to measure the ability of subjects to evaluate component actions of

social situations. Generally, a script task consists of free recall, frequency judgment, and sequencing of events in the schema of daily activities, such as dining at restaurants or shopping at supermarkets (Chan et al., 1999; Matsui et al., 2006). One of the most consistent findings with the script tasks has been that patients with schizophrenia perform worse on judging the events that sometimes happen (middle frequency events), rather than those that usually or rarely happen (prominent events), in the Frequency Judgment Task (Chan et al., 1999; Matsui et al., 2006).

Altered composition of phospholipids, a major component of neural membranes, has been suggested to be related to the pathophysiology of schizophrenia (Horrobin, 1998). Among the constituents of phospholipids, saturated fatty acids, e.g. palmitic acid (14:0, PA) and stearic acid (16:0, SA), as well as monounsaturated fatty acids, e.g. oleic acid (18:1 n-9, OA) and nervonic acid (24:1, NA), can be synthesized de novo. On the other hand, essential polyunsaturated fatty acids (EPUFAs) must be ingested in the diet. These include: linoleic acid (18:2 n-6, LA), dihomogammalinolenic acid (20:3 n-6, DGLA), and arachidonic acid (20:4 n-6, AA) as the n-6 series; and eicosapentaenoic acid (20:5 n-3, EPA), docosapentaenoic acid (22:5 n-3, DPA), and docosahexaenoic acid (22:6n n-3, DHA) as the n-3 series (Horrobin, 1998; Fenton et al., 2000).

Since EPUFA levels in erythrocyte membranes have been shown to reflect EPUFA composition in the brain (Connor et al., 1990), various studies have been conducted to evaluate the change in this peripheral measure of EPUFAs in patients with schizophrenia (for review, see Fenton et al., 2000). These studies indicate an overall decrease in the concentrations of the above-mentioned EPUFAs in patients compared with normal control subjects (Vaddadi et al., 1989; Glen et al., 1994; Yao and van Kammen, 1994; Peet et al., 1995; Khan et al., 2002; Arvindakshan et al., 2003a,b). Diet, medication status, or smoking may not be associated with alterations in the EPUFA levels (Yao and van Kammen, 1994; Yao et al., 1994a,b; Doris et al., 1998; Assies et al., 2001; Reddy et al., 2004). On the other hand, erythrocyte membrane levels of EPUFAs, such as AA, have been shown to be correlated with the severity of psychotic symptoms (Peet and Horrobin, 2002, but see Assies et al., 2001).

In addition to the relationship between abnormal EPUFA metabolism and schizophrenia, previous studies also suggest altered fatty acid compositions in patients with depression (Maes et al., 1996, 1999) or autism (Vancassel et al., 2001), as well as clinical benefits from the administration of EPUFAs to subjects with border-line personality disorder (Zanarini and Frankenburg, 2003) or antisocial behavior (Gesch et al., 2002). Since these disorders are characterized by disturbances of social abilities, it is hypothesized that decreased EPUFA levels may be associated with impaired performance on neuropsychological tests measuring social cognition.

So far, there has been little study on the relationship between abnormal EPUFA metabolism and disturbances of cognitive performance relevant to social functions in subjects with schizophrenia. The primary purpose of the present study, therefore, was to determine whether decreased erythrocyte membrane EPUFA levels would be correlated selectively with poor performance on script tasks, but not with other aspects of cognitive dysfunctions, in patients with schizophrenia. We also sought to determine if EPUFA concentrations are related to the severity of psychotic symptoms.

2. Methods

2.1. Subjects

Twenty-five chronically-ill out-patients (male/female = 14/11) meeting DSM-IV criteria for schizophrenia entered the study. They were recruited from the Outpatient Clinic of the University Hospital of Toyama. All available clinical information and data were obtained from a structured clinical interview (Sumiyoshi et al., 2001a,b). Subjects were diagnosed by a consensus of at least two experienced psychiatrists. Patients known to be abusing alcohol or other illicit drugs, or those with epilepsy, brain damage, or neurologic disorders, were excluded from the study. This study was carried out in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained after the explanation of the study. The protocol was approved by the Institutional Review Board of the University of Toyama School of Medicine. Sixteen patients were treated with the following first generation (typical) antipsychotic drugs: haloperidol ($N=8$), nemonapride ($N=4$), zotepine ($N=2$), chlorpromazine ($N=1$), and levomepromazine ($N=1$); nine patients were neuroleptic-free. The mean (S.D.) daily haloperidol-equivalent dose (mg) for the patients on medications was 6.9 (7.3). Patients were assessed with the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) by psychiatrists or well-trained clinical psychologists. Interrater reliability was >0.80 (Sumiyoshi et al., 2001a,b). Blood samples were obtained from these subjects between 09:30 and 10:00 h after an overnight fast.

Blood samples were also obtained from 32 age- and gender-matched healthy volunteers (male/female = 18/