Inverse association between 18-carbon trans fatty acids and intelligence quotients in smoking schizophrenia patients

Szimonetta Lohner [a,*], Judit Vágási [a], Tamás Marosvölgyi [a], Tamás Tényi [b], Tamás Decsi [a]

[a] Department of Pediatrics, University of Pécs, József A. u. 7, H-7623 Pécs, Hungary
[b] Department of Psychiatry and Psychotherapy, University of Pécs, Pécs, Hungary

ARTICLE INFO

ABSTRACT

This study aimed to investigate polyunsaturated (PUFA) and trans isomeric fatty acid status in schizophrenia patients. Fatty acid composition of plasma phospholipids (PL) and triacylglycerols (TG) was analyzed by gas chromatography in 29 schizophrenia patients and 15 healthy controls. We found no difference in PL n-3 fatty acid status between the two groups, while the values of 22:5n-6 were significantly higher in patients with schizophrenia than in controls. In TG, values of docosatrienoic acid (20:3n-3) and docosapentaenoic acid (20:5n-3) were significantly higher in schizophrenia patients than in controls. We found no difference in the trans fatty acid status between patients and controls. In smoking schizophrenia patients significant negative correlations were detected between Wechsler adult full-scale intelligence quotients and values of total trans fatty acids in PL lipids, whereas no such correlation was seen either in non-smoking schizophrenia patients, or in healthy controls. While data obtained in the present study fail to furnish evidence for n-3 PUFA supplementation to the diet of patients with schizophrenia, they indicate that in smoking schizophrenia patients high dietary exposure to trans fatty acids is associated with lower intelligence quotients.

© 2013 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Polyunsaturated fatty acids (PUFAs) are important components of cell membranes, like erythrocyte membranes and neuronal membranes, and play an important role in appropriate functioning of the central nervous system (Chang et al., 2009). The presently available data of the literature suggest that the metabolism of PUFAs is altered in patients with schizophrenia; hence, the altered neuronal membrane structure and metabolism might contribute to some of the symptoms of schizophrenia. Erythrocyte membrane lipid fatty acid composition may serve as surrogate parameter of fatty acid composition of other cell membranes, so erythrocyte membrane lipid composition of patients with schizophrenia was investigated extensively. In these studies, decreased levels of erythrocyte membrane DHA (docosahexaenoic acid, 20:6n-3) were described almost consequently (Arvindakshan et al., 2003; Assies et al., 2001; Evans et al., 2003; Kale et al., 2008; Kemperman et al., 2006; Khan et al., 2002; Ranjekar et al., 2003; Reddy et al., 2004; Sethom et al., 2010).

In contrast, the potential role of trans fatty acids in schizophrenia has not been explored so far. Trans fatty acids are unsaturated fatty acids containing double bonds in trans stereoisomeric configuration; their excessive dietary intake is a significant risk factor for cardiovascular events (Imamura et al., 2012; Salter, 2013). In several human studies, significant inverse correlation between plasma long-chain PUFAs (LCPUFAs) and trans fatty acids was reported (Szabó et al., 2007; Decsi et al., 2002, 2001; Decsi and Koletzko, 1995; Koletzko, 1992). Moreover, trans fatty acids in umbilical vein wall lipids were significantly inversely associated with the neurologic optimality score at the age of 18 months (Bouwstra et al., 2006), even after adjustment for LCPUFA, indicating thereby direct relationship between trans fatty acids and neurological function. However, in patients with schizophrenia we found no data on the potential association of trans fatty acids with neurological parameters.

Because the structure and metabolism of neural cell membranes depends on the availability of fatty acids, in this case-controlled study we decided to determine plasma PUFA, LCPUFA and trans fatty acid status in patients with schizophrenia. Furthermore, we investigated the relationship between psychopathology of schizophrenia patients and fatty acid composition of plasma lipids.

2. Methods

2.1. Study subjects

Subjects were recruited in the Department of Psychiatry and Psychotherapy, University of Pécs, Pécs, Hungary. All available clinical information and data were obtained from structured clinical interviews. Inclusion criteria for the present study were: age between 18 and 89 years; all patients meet the DSM-IV-TR diagnostic criteria for schizophrenia (Diagnostic and Statistical Manual of Mental Disorders,

---

2000). Exclusion criteria were: (1) simultaneous presence of a serious chronic illness (e.g. diabetes mellitus, hepatitis or chronic intestinal disease, neurologic disorder, epilepsy or brain damage), (2) severe under- or malnutrition, (3) use of fatty acid supplements or any other dietary supplements, (4) alcohol or substance abuse or dependence, and (5) lipid metabolism disorders. Control subjects were healthy, aged-matched persons recruited from the hospital staff (all were manual workers). This study was carried out in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from all subjects after the explanation of the study. It is to be noted that all patients included into the present study were still symptomatic despite exposure to antipsychotic drugs: 24 patients were in the acute phase of the disease, while five patients were in remission. Symptomatic remission in schizophrenia was established according to the criteria from Andreasen et al. (2005). Only two patients were neuroleptic-free at enrollment.

2.2. Clinical assessment

Patients were evaluated for psychopathology using the Positive and Negative Syndrome Scale (PANSS), which is a brief clinician-rated scale designed to assess mental state and severity of psychopathology. There are 30 items, each item is scored on a scale of one (absent) to seven (extreme). The PANSS can be divided into three sub-scales measuring severity of (a) general psychopathology, (b) positive symptoms (PANSS-P), and (c) negative symptoms (PANSS-N). A low score indicates low level of psychopathology.

The Wechsler adult intelligence scale (WAIS) was used to measure the intelligence of the participants. It elicits three intelligence quotient scores; all three are standardized in such a way that the scores have a mean of 100 and a standard deviation of 15. The full-scale IQ is an overall intelligence quotient. The verbal IQ is derived from scores on seven of the subtests: information, digit span, vocabulary, arithmetic, comprehension, similarities and letter-number sequencing. The performance IQ is derived from scores on the remaining seven subtests: picture completion, picture arrangement, block design, object assembly, digit symbol, matrix reasoning and symbol search.

2.3. Plasma lipid analysis

Laboratory analysis was carried out in the chromatograph laboratory at the Department of Pediatrics, Pécs. The blood samples collected into tubes containing 2 mg/ml EDTA were centrifuged immediately and stored at $-80\ ^{\circ}C$ until analysis. Lipids were extracted from 150 μl serum with the mixture of 3 ml chloroform and 1 ml methanol. The mixture received was centrifuged at 3000/min for 10 min.

Plasma samples were fractioned into phospholipids (PL), triacylglycerols (TG) and cholesterol esters (ST) on thin-layer chromatography silica gel plates with hexan/diethil-ether/chloroform/acetic acid (21:6:3:1). Then the PL and TG fractions were transesterified with methanol and hydrochloric acid, and the methyl esters were identified by high-resolution gas–liquid chromatography.

2.4. Statistical analysis

Fatty acid results were expressed as percentage (w/w%) of all fatty acids detected with a chain length between 12 and 24 carbon atoms. Data were analyzed by using the program Windows SPSS and were expressed as median and interquartile range, because distributions were not equal to normal distribution, especially in case of fatty acids present at low concentrations. Results were compared with Mann–Whitney test, the level of significance chosen was $p < 0.05$. Healthy controls were age and sex matched, but no adjustment in form of a multivariate analysis was done.

We used Spearman rank correlation to analyze associations between fatty acid values and psychopathological indices.

3. Results

Clinical characteristics of participants are shown in Table 1, while psychometric measures of both schizophrenia patients and control subjects are shown in Table 2. Except the disease-related parameter of Positive and Negative Syndrome Scale, no other difference was seen between patients and controls.

Fatty acid compositions of the PL and TG fractions are shown in Table 3. There was no difference between the schizophrenia patients and control subjects in the contribution of n-3 fatty acids to the lipid composition of the PL fraction while the values of total n-6 PUFAs and that of the n-6 LCPUFA, docosapentaenoic acid (22:5n-6) were significantly lower in patients with schizophrenia than in the control subjects. We found difference neither in the n-3/n-6 PUFA ratio nor in the n-3/n-6 LCPUFA ratio between the

Table 1
Characteristics of participants.

	Schizophrenia ($n=29$)	Control ($n=15$)
Sex (male/female)	14/15	7/8
Age (years)	36.0 (10.1)	35.6 (7.0)
Weight (kg)	77.1 (20.8)	74.1 (17.8)
Height (cm)	170.8 (6.7)	171.8 (10.7)
Body mass index (kg/m^2)	26.4 (6.6)	24.9 (4.2)
Triacylglycerol (mM/L)	2.07 (1.47)	2.29 (1.47)
Total cholesterol (mM/L)	4.94 (1.08)	5.08 (0.86)
HDL cholesterol (mM/L)	1.19 (0.25)	1.15 (0.28)
LDL cholesterol (mM/L)	3.17 (0.66)	3.20 (0.79)
Current smoker (yes/no)	12/17	5/10

Data are mean (S.D.).

Table 2
Psychopathological indices in schizophrenia patients.

	Schizophrenia ($n=29$)	Control ($n=15$)
PANSS		
PANNS-P (max. 49)	14.28 (4.32)	–
PANNS-N (max. 49)	22.48 (5.38)	–
Total PANNS (max. 210)	71.83 (12.87)	–
Wechsler adult intelligence scale		
Full-scale IQ	99.59 (12.35)	98.13 (14.58)
Verbal IQ	100.52 (12.25)	96.67 (13.09)
Performance IQ	99.76 (13.23)	100.80 (15.6)

PANSS: Positive and Negative Syndrome Scale, P: positive symptoms, N: negative symptoms. Data are mean (S.D.).

two groups. In the TG fraction, n-6 PUFA values did not differ between the schizophrenia and the control groups, but the values of eicosatrienoic acid (20:3n-3), docosapentaenoic acid (22:5n-3) and total n-3 LCPUFAs were significantly higher in schizophrenia patients than in the control subjects.

We divided both the patient and the control groups into subgroups according to their smoking habits. In schizophrenic smokers PANSS negative scores were significantly higher ($p=0.01$) than in non-smokers. In smoking subjects, there were no differences between the plasma PL n-3 or n-6 fatty acid values of schizophrenia patients ($n=12$) and control ($n=5$) subjects; whereas in the non-smoking subgroup the values of linoleic acid (18:2n-6) were significantly lower in schizophrenia patients ($n=17$) as compared to the values seen in controls ($n=10$).

There was no significant difference between schizophrenia patients and controls either in plasma PL and TG trans fatty acids. The relationship between intelligence quotient (IQ) and values of plasma phospholipid and triacylglycerol fatty acids in smoking schizophrenia patients are shown in Table 4. We found significant negative correlation between IQ and trans fatty acids in the smoking subgroup, while no such correlation could be detected either in the non-smoking schizophrenia subgroup, or in the control group.

4. Discussion

The contribution of LCPUFA to the fatty acid composition of erythrocyte membrane lipids in schizophrenia patients was investigated in several studies. In most of the studies DHA levels were found to be decreased, while values of AA were either decreased (Evans et al., 2003; Kemperman et al., 2006; Khan et al., 2002; Reddy et al., 2004; Sethom et al., 2010) or no significant difference was found in its values between schizophrenia patients and control subjects (Arvindakshan et al., 2003; Assies et al., 2001; Kale et al., 2008; Ranjekar et al., 2003).