European Psychiatry 39 (2017) 51–56

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Fatty acid composition of the postmortem corpus callosum of patients with schizophrenia, bipolar disorder, or major depressive disorder

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ARTICLE INFO

Article history:
Received 1st March 2016
Received in revised form 22 April 2016
Accepted 13 May 2016
Available online 5 November 2016

Keywords:
Schizophrenia
Bipolar disorder
Major depressive disorder
Polyunsaturated fatty acids
Postmortem brain
Corpus callosum

ABSTRACT

Background: Studies investigating the relationship between n-3 polyunsaturated fatty acid (PUFA) levels and psychiatric disorders have thus far focused mainly on analyzing gray matter, rather than white matter, in the postmortem brain. In this study, we investigated whether PUFA levels showed abnormalities in the corpus callosum, the largest area of white matter, in the postmortem brain tissue of patients with schizophrenia, bipolar disorder, or major depressive disorder.
Methods: Fatty acids in the phospholipids of the postmortem corpus callosum were evaluated by thin-layer chromatography and gas chromatography. Specimens were evaluated for patients with schizophrenia ($n = 15$), bipolar disorder ($n = 15$), or major depressive disorder ($n = 15$) and compared with unaffected controls ($n = 15$).
Results: In contrast to some previous studies, no significant differences were found in the levels of PUFAs or other fatty acids in the corpus callosum between patients and controls. A subanalysis by sex gave the same results. No significant differences were found in any PUFAs between suicide completers and non-suicide cases regardless of psychiatric disorder diagnosis.
Conclusions: Patients with psychiatric disorders did not exhibit n-3 PUFAs deficits in the postmortem corpus callosum relative to the unaffected controls, and the corpus callosum might not be involved in abnormalities of PUFA metabolism. This area of research is still at an early stage and requires further investigation.

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1. Background

The causes of psychiatric disorders are not fully understood, although emerging evidence suggests the involvement of brain lipid metabolism, especially in relation to polyunsaturated fatty acids (PUFAs) [1–3]. Some postmortem brain studies [4–8], but not all [9–15], have found an altered (decreased) level of n-3 PUFAs, particularly docosahexaenoic acid (DHA), in the frontal cortex in psychiatric disorder (especially in the orbitofrontal cortex [4–6]). No significant differences in DHA have been found in the hippocampus [16], amygdala [17], entorhinal cortex [18], inferior temporal cortices [10], superior temporal gyrus [19], or caudate [20].

In recent years, attention has been focused on the potential role of the corpus callosum in psychiatric disorders. Previous studies have suggested important roles for this area in neurobiological and/or morphological models of schizophrenia [21], bipolar disorder [22], and major depressive disorder [23]. The corpus callosum is the largest white matter fiber tract in the brain and not only connects the majority of axonal transmissions between the two cerebral hemispheres, but also helps interhemispheric information transfer [24]. A preclinical study in rats showed that a diet deficient in essential fatty acids (which consequently decreased n-3 PUFA level by 52% in light myelin and by 70% in heavy myelin) did not cause an obvious decrease in the degree of myelination but did change the myelin morphologically (causing vacuoles) [25]. Another study in rats showed that intracerebroventricular injection of n-3 PUFAs stimulated the expression of specific myelin proteins in nearly all brain regions [26].

Regarding n-3 PUFAs specifically, a few studies have found a correlation between peripheral n-3 PUFAs and white mater integrity in psychiatric disorders. Lower erythrocyte total n-3 PUFA levels were associated with lower white mater integrity measured by magnetic resonance imaging (including in the corpus

Abbreviations: AA, arachidonic acid; CVD, cardiovascular disease; DHA, docosahexaenoic acid; PMI, postmortem interval; PUFAs, polyunsaturated fatty acids.

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http://dx.doi.org/10.1016/j.eurpsy.2016.05.007
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callosum) in recent-onset psychotic disorder [27], although significant associations were seen individually only for docosapentaenoic acid (n-3) and arachidonic acid (AA), not DHA [27]. In the case of bipolar disorder (not specifically focusing on white matter), a 4-week intervention study with n-3 fatty acids showed significantly reduced brain water proton transverse relaxation times (T2), indicating increased membrane fluidity [28]. Lastly, in the case of major depressive disorder, a 6-week intervention study with n-3 PUFAs revealed that an increase in plasma DHA correlated with an increase in fractional anisotropy (high fractional anisotropy indicates healthy white matter) in a more anterior region encompassing the genu and body of the corpus callosum, and in the anterior corona radiata and cingulum bilaterally [29]. In the depressed group of that study (prior to supplementation), plasma phospholipid DHA positively correlated with fractional anisotropy in the body of the corpus callosum [29].

Nervonic acid, a monounsaturated fatty acid, is also an interesting candidate in the pathology of schizophrenia. Amminger et al. found in a 12-month cohort study that lower erythrocyte levels of nervonic acid predicted the development of psychotic disorder [30]. Given that nervonic acid is a major component of the myelin sheath, they speculated that the reduced levels could reflect suboptimal myelin status in individuals at ultra-high risk who eventually developed psychotic disorder. This is supported by a later imaging study showing that erythrocyte nervonic acid was positively associated with white matter integrity (fractional anisotropy) [27]. For further analysis, we decided to measure the fatty acid composition of the corpus callosum from patients with schizophrenia, bipolar disorder, or major depressive disorder and compared it with that of unaffected controls.

2. Materials and methods

2.1. Postmortem corpus callosum samples

Brain tissue samples were provided by the Victorian Brain Bank Network (VBBN), Florey Institute for Neuroscience and Mental Health. Following study approval by the Ethics Committee of RIKEN Brain Science Institute and the University of Toyama (No. 22-56), approval for tissue collection was granted by the Ethics Committee of the Victorian Institute of Forensic Medicine and that for tissue supply was granted by the Tissue Access Committee of the VBBN. The tissue samples were from patients with schizophrenia ($n = 15$), bipolar disorder ($n = 15$), or major depressive disorder ($n = 15$) and from healthy (non-pathological) controls ($n = 15$). Blocks of the genu of corpus callosum were cut and rapidly frozen to −80 °C as described previously [31] and then sent to RIKEN Brain Science Institute and on to the University of Toyama.

As described in our previous study using the same tissue samples [14], tissue was taken from cadavers stored at 4 °C within 5 h of death. Age at death, sex, brain pH, and postmortem interval (PMI, hours) were examined [32]. PMI was defined as the period from time of death to autopsy in cases where death had been witnessed; in cases it had not, the time of death was taken as the mid-point between the time last seen alive and the time found dead (maximum duration between the mid-point and the time found dead was set at 5 h) [33]. Psychiatric diagnosis was made after reviewing the clinical records. This diagnosis was made according to DSM-IV criteria and with the Diagnostic Instrument for Brain Studies that allows for a consensus psychiatric diagnosis to be made after death [34,35]. For all non-psychiatric cases, case histories were extensively reviewed and a neuropsychopharmacological profile was obtained. In addition, treating clinicians and family members were questioned about the patients to exclude any history of psychiatric illness. Table 1 shows the demographics of the patients and unaffected controls whose postmortem samples were analyzed in this study.

2.2. Tissue preparation and lipid extraction

The methods are described in our previous study [14]. Briefly, frozen sections of corpus callosum tissue were homogenized in ice-cold saline and the aliquots used for lipid analysis. Following total lipid extraction [36], the total phospholipid fractions were separated by thin-layer chromatography. After transmethylation with HCl-methanol, the fatty acid composition was analyzed by gas chromatography (GC-2014 Shimadzu Corporation, Kyoto, Japan) with a DB-225 capillary column (length 30 m; internal diameter 0.25 mm; film 0.25 μm; J&M Scientific, Folsom, CA), controlled using the gas chromatography software GC-solution version 2.3 (Shimadzu Corporation). Fatty acids were individually expressed as percentage area of total fatty acids.

2.3. Statistical analysis

Characteristics of the postmortem corpus callosum samples are expressed as means ± SD. Differences between groups were examined using the Chi^2 test for categorical variables and one-way ANOVA for continuous variables. Bonferroni post hoc tests were performed for significant results found by one-way ANOVA. We used the Kruskal–Wallis test (Table 2) and ANOVA (Supplementary Table 1) to compare individual fatty acids between the four groups. We did not perform corrections for multiple comparisons because this was an exploratory study involving a small number of postmortem samples. Chlorpromazine equivalents were used to calculate doses of antipsychotic drugs. Further comparisons of individual fatty acids adjusted for age, sex, PMI, use of antipsychotic, and duration of specimen storage (years) between the four groups were made by analysis of covariance (ANCOVA). Spearman's rank correlation test was used to calculate correlation coefficients between each fatty acid level and age, PMI, pH, and chlorpromazine equivalents. Fisher's exact test was used to compare the prevalence of suicide between groups. The Mann–Whitney U-test was use for single comparisons between suicide completers and non-suicide cases and between men and women. Statistical significance was set at $P < 0.05$. Data were analyzed using the statistical software SPSS, version 19.0 (IBM Japan, Tokyo, Japan).

Table 1
Characteristics of patients with psychiatric disorder and unaffected controls.

	Control $n = 15$	Schizophrenia $n = 15$	Bipolar disorder $n = 15$	Major depressive disorder $n = 15$	*P*-value
Age at death (years)	57 ± 13	58 ± 14	58 ± 14	57 ± 12	0.99
Sex (male/female)	8/7	8/7	8/7	8/7	1.00
Postmortem interval (h)	43 ± 18	43 ± 13	36 ± 15	42 ± 17	0.61
Duration of specimen period (years)	12.3 ± 5.6	14.9 ± 4.3	12.8 ± 4.4	9.5 ± 3.9	0.02
Brain tissue pH	6.34 ± 0.23	6.18 ± 0.27	6.26 ± 0.24	6.52 ± 0.19	0.002
Number of suicides[a]	0	3	4	13	< 0.0001

P-value: 2 × 4 Chi^2 test for categorical variables and one-way ANOVA for continuous variables.
[a] One datum was missing in the major depressive disorder group for cause of death.

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