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Fatty acid composition in the postmortem amygdala of patients with schizophrenia, bipolar disorder, and major depressive disorder

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ABSTRACT

Previous studies with postmortem brain tissues showed abnormalities in n-3 polyunsaturated fatty acids (PUFAs) in the orbitofrontal cortex of individuals with schizophrenia and mood disorders. However, in the hippocampus, we were not able to find any significant differences in PUFAs except for small differences in n-6 PUFAs. In the present study we investigated levels of PUFAs in the amygdala of postmortem brains from patients with schizophrenia, bipolar disorder, and major depressive disorder (MDD) compared with those of unaffected controls. Amygdala samples from patients with schizophrenia ($n = 15$), bipolar disorder ($n = 15$), or MDD ($n = 15$), and controls matched for age, sex, and five other confounding factors ($n = 15$) were analyzed for fatty acid composition by gas chromatography. In contrast to previous studies of the orbitofrontal cortex and hippocampus, we were unable to find any significant differences in major PUFAs. The relative compositions of docosahexaenoic acid (DHA), the major n-3 PUFA, were 10.0 ± 1.1%, 10.0 ± 1.3%, 9.3 ± 1.3%, and 9.7 ± 1.1%, respectively, in patients with schizophrenia, bipolar disorder, and MDD and unaffected controls (not significantly different). The corresponding relative compositions of arachidonic acid (AA), the major n-6 PUFA, were 9.0 ± 0.8%, 9.2 ± 0.5%, 9.4 ± 0.7%, and 9.4 ± 0.7%, respectively (not significantly different). Significant differences were found in some of the other fatty acids. In particular, we found a 6.5% increase in palmitic acid and 6.2% decrease in oleic acid in patients with MDD compared to controls. With regard to schizophrenia, there was an 8.0% decrease in docosatetraenoic acid compared to controls. In conclusion, the changes in DHA and/or AA seen in orbitofrontal cortex and hippocampus were not observed in amygdala. These changes may be specific to particular brain regions.

1. Introduction

An emerging body of evidence from epidemiological studies indicates that patients with major depressive disorder (MDD), bipolar disorder, and schizophrenia have reduced amounts of n-3 polyunsaturated fatty acids (PUFAs) in peripheral tissues such as red blood cells, serum, and plasma (Freeman et al., 2006; Lin et al., 2010). The most recent meta-analysis of randomized controlled trials of n-3 PUFAs in MDD revealed only a small, non-significant alleviation of depressive symptoms (Bloch and Hannestad, 2011). However, another meta-analysis showed a significant benefit when limited to studies of supplements with eicosapentaenoic acid accounting for more than 60% of the total n-3 PUFA content (Sublette et al., 2011). With regard to bipolar disorder alone, a meta-analysis showed that depressive, but not manic, symptoms might be improved by adjunctive use of n-3 PUFAs (Sarris et al., 2011). With regard to schizophrenia, the latest meta-analysis of four clinical trials showed no significant benefit in n-3 PUFAs (Freeman et al., 2006).

Clinical consequence of abnormalities in n-3 PUFAs in these psychiatric diseases may be pathophysiologically explained as follows. Firstly, serotonergic neurotransmission is important in psychiatric diseases. Olsson et al. (1998) reported that a diet low in n-3 PUFAs decreased serotonin and 5-hydroxyindolacetic acid (5-HIAA) concentrations in rat. n-3 PUFA deficiency was associated with significant elevations in cortical serotonin 5-HT2A receptor binding density (Delion et al., 1996). Kodas et al. (2004) found that deficits in fenfluramine-induced serotonin release in the rat hippocampus could be normalized when dietary n-3 PUFA fortification was initiated. In an observational study, Hibbeln et al. (1998)

Abbreviations: AA, arachidonic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; MDD, major depressive disorder; PUFAs, polyunsaturated fatty acids; SMRI, the Stanley Medical Research Institute.

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found that higher plasma concentrations of DHA and AA predicted higher concentrations of cerebrospinal fluid (CSF) 5-HIAA among healthy subjects. All these observations indicate an important relationship between n-3 PUFAs and brain functions. Secondly, brain derived neurotrophic factor (BDNF) is essential for neuronal plasticity and the development of the central nervous system, and is widely implicated in psychiatric diseases (Autry and Monteggia, 2012). Dietary n-3 PUFAs have been found to increase the levels of BDNF in rat hippocampus (Wu et al., 2004, 2008). We have also found that n−3 PUFA administration to patients who were at high risk of posttraumatic distress disorder increased their serum level of BDNF (Matsuoka et al., 2011). Thirdly, regulation of corticotropin-releasing hormone (CRH) might be influence by PUFAs. Prostaglandin E2, of which production is depressed by n-3 PUFAs, increases the RNA expression of CRH (Bugajski, 1996). In this context, Hibbeln et al. (2004) assessed CSF and plasma for CRH and fatty acid compositions, respectively, among 21 perpetrators of domestic violence. They found that lower plasma DHA alone predicted greater CSF CRH levels. Fourthly, dopaminergic function is known to be affected by n-3 PUFAs in animal studies (Zimmer et al., 1998, 2002). Lastly, DHA plays an important role in the brain not only via anti-apoptotic and neurotrophic pathways but also through anti-neuroinflammatory pathways (Orr and Bazinet, 2008).

All the discussion above raises the question of whether alteration of the level of PUFAs is a universal phenomenon throughout the brain of patients with psychiatric disorders. We have recently investigated n-3 PUFAs in the postmortem hippocampus from subjects with schizophrenia ($n = 35$) and bipolar disorder ($n = 34$), and from unaffected controls ($n = 35$), but could find no significant differences in PUFAs between the three groups, except for small differences in n-6 PUFAs (i.e., arachidonic acid (AA) and docosapentaenoic acid (DPA)) (Hamazaki et al., 2010).

The amygdala has a wide variety of functions such as cognition, memory consolidation, and control of affective behaviors (Phelps, 2004; Siever, 2008). Morphometric and histological abnormalities have been found in the amygdala of patients with psychiatric disorders. Meta-analyses of imaging studies showed volume reductions in the amygdala in patients with schizophrenia (Wright et al., 2000), bipolar disorder (Usher et al., 2010), and MDD (Bora et al., 2011). Case-control studies of post-mortem brains also showed reductions in both volume and neuron number in the amygdala of patients with schizophrenia (Kreczmanski et al., 2007), bipolar disorder (Berretta et al., 2007), and MDD (Altshuler et al., 2010; Bowley et al., 2002; Hamidi et al., 2004).

As discussed above, morphological abnormalities of the amygdala in psychiatric disorders have been described, but there are no data regarding the fatty acid profile. In this study, we investigated whether there were any changes in PUFAs in the amygdala of patients with schizophrenia, bipolar disorder, and MDD compared to unaffected controls.

2. Methods

2.1. Postmortem amygdala tissue samples

Brain tissues were obtained from the Stanley Medical Research Institute (SMRI; Rockville, MD, USA). There were 15 samples each for patients with schizophrenia, bipolar disorder, or MDD, and control individuals matched for age, sex, race, postmortem interval, brain pH, and laterality of hemisphere.

The selection, clinical information, diagnosis, and processing of brain tissue have been described previously (Torrey et al., 2000). Briefly, specimens were collected, with informed consent from the next-of-kin, by participating medical examiners. The specimens were collected, processed, and stored in a standardized way (Torrey et al., 2000). Diagnoses were made by two senior psychiatrists, using DSM-IV criteria and based on medical records and, when necessary, telephone interviews with family members. After the fatty acid data were submitted to SMRI, they returned the diagnostic status and a range of clinical variables for our analysis. Patients' clinical and demographic characteristics are summarized in Table 1.

2.2. Tissue preparation and lipid extraction

Frozen sections of amygdala tissues were scraped from three consecutive slides (14 μm thick) on dry ice and homogenized in ice-cold phosphate-buffered saline (pH 7.4), and aliquots were used for lipid analysis. Total lipids were extracted according to the method of Bligh and Dyer (Bligh and Dyer, 1959). 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) equipped with a DB-225 capillary column (length, 30 m; internal diameter, 0.25 mm; film 0.25 μm; J&M Scientific, Folsom, CA). The entire system was controlled using the gas chromatography software GC-solution version 2.3 (Shimadzu Corporation, Kyoto, Japan). Fatty acids were expressed as percentage area of total fatty acids. The intra-assay and inter-assay coefficients of variance were 1.7% and 6.3% for AA, and 1.9% and 7.7% for docosahexaenoic acid (DHA), respectively.

2.3. Statistical analysis

Data are expressed as means ± SD. Clinical data and characteristics of samples were compared among groups using the chi-square test for categorical variables and one-way ANOVA for continuous variables. Before further analyses of each fatty acid, the normality of distribution was checked with the Kolmogorov–Smirnov test. Because some fatty acids were not normally distributed, we used the Mann–Whitney *U* test with Bonferroni's adjustment for comparison of individual fatty acids between control subjects and patients with

Table 1
Subject characteristics.

	Control $n = 15$	Schizophrenia $n = 15$	Bipolar disorder $n = 15$	Major depressive disorder $n = 15$	*p*-value
Age (years at death)	48 ± 11	45 ± 13	42 ± 12	47 ± 9	n.s.
Gender (male/female)	9/6	9/6	9/6	9/6	n.s.
Postmortem interval (hours)	24 ± 10	34 ± 15	33 ± 16	27 ± 11	n.s.
Brain tissue pH	6.27 ± 0.24	6.16 ± 0.26	6.18 ± 0.23	6.18 ± 0.22	n.s.
Number of Suicide	0	4	9	7	0.003
Alcohol abuse severity (low/high)	15/0	12/3	10/5	9/6	0.0497
Substance abuse severity (low/high)	15/0	12/3	13/2	12/3	n.s.
Side of brain hemisphere (left/right)	8/7	9/6	7/8	9/6	n.s.
Brain weight (g)	1501 ± 164	1472 ± 108	1441 ± 172	1462 ± 142	n.s.

p value: chi-square test for categorical variables and one-way ANOVA for continuous variables.