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Abnormalities in the fatty acid composition of the postmortem entorhinal cortex of patients with schizophrenia, bipolar disorder, and major depressive disorder

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ABSTRACT

Previous studies of postmortem orbitofrontal cortex have shown abnormalities in levels of *n*−3 polyunsaturated fatty acids (PUFAs), especially docosahexaenoic acid (DHA), in individuals with schizophrenia, bipolar disorder, and major depressive disorder (MDD). We have previously measured PUFA levels in the postmortem hippocampus from patients with schizophrenia or bipolar disorder and control subjects; however, we found no significant differences between the groups except for small changes in *n*−6 PUFAs. Furthermore, our study of the postmortem amygdala showed no significant differences in major PUFAs in individuals with schizophrenia, bipolar disorder, or MDD in comparison with controls. In the present study, we investigated whether there were any changes in PUFAs in the entorhinal cortexes of patients with schizophrenia ($n=15$), bipolar disorder ($n=15$), or MDD ($n=15$) compared with unaffected controls ($n=15$) matched for characteristics including age and sex. In contrast to previous studies of the orbitofrontal cortex and hippocampus, we found no significant differences in major PUFAs. However, we found a 34.3% decrease in docosapentaenoic acid (DPA) (22:5*n*−3) in patients with MDD and an 8.7% decrease in docosatetraenoic acid (22:4*n*−6) in those with schizophrenia, compared with controls. Changes in PUFAs in patients with these psychiatric disorders may be specific to certain brain regions.

1. Introduction

A growing body of epidemiologic evidence has shown abnormalities in the levels of *n*−3 polyunsaturated fatty acids (PUFAs) in peripheral tissues in psychiatric disorders. The first substantially large investigation comparing erythrocyte membrane fatty acids between the first-episode drug-naive psychotic patients, chronic medicated-schizophrenia, and normal controls was conducted in the United States (Khan et al., 2002). The percentage distribution values of arachidonic acid (AA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) (*n*−3) were all low in patients with psychosis, especially in the first-episode drug-naive group. These results were confirmed by the other group (Evans et al., 2003), and they found that the level of peripheral DHA was normalized by 6 months of antipsychotic treatment. As for bipolar disorder, low level of *n*−3 PUFAs in peripheral was also seen (Chiu et al., 2003; Ranjekar et al., 2003; McNamara et al., 2010). Major depressive disorder (MDD) is probably the most studied field in *n*−3 PUFA area. Lin et al. (2010) conducted meta-analyses of 14 studies comparing the peripheral levels of *n*−3 PUFAs between patients with depression and control subjects, and found that they were significantly lower in patients with depression (even much lower in those patients with DSM-defined MDD).

Although *n*−3 PUFA levels in plasma and red blood cells are known to reflect those of the brain (Tu et al., 2013), studies of the postmortem brain in this field are still scarce and the results inconsistent. McNamara et al. investigated the fatty acid composition of postmortem orbitofrontal cortex from patients with schizophrenia (McNamara et al., 2007b), bipolar disorder (McNamara et al., 2008), or MDD (McNamara et al., 2007a) and found that amounts of DHA were significantly lower by 20%, 24%, and 22%, respectively, in patients compared with control subjects. In contrast to their findings, we previously found no decrease in DHA in the postmortem hippocampus of patients with schizophrenia or bipolar disorder (Hamazaki et al., 2010). Levels of AA and DPA (*n*−6) in the schizophrenia group were significantly lower (−5.3% and −10.6%, respectively) than in the control group. In patients with bipolar disorder, only DPA (*n*−6) was significantly lower (−7.5%) than in

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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control subjects. There were no decreases in DHA or AA levels in the postmortem amygdala in patients with schizophrenia, bipolar disorder, or MDD (Hamazaki et al., 2012). However, we found an 8.0% decrease in docosatetraenoic acid (*n*−6) (22:4*n*−6) in patients with schizophrenia as well as a 6.5% increase in palmitic acid (16:0) and a 6.2% decrease in oleic acid (18:1*n*−9) in those with MDD.

The entorhinal cortex is part of the medial temporal lobe and regulates memory. It is an important relay station between the sensory cortex and the hippocampus (Krimer et al., 1997). The entorhinal cortex is believed to be involved in the pathophysiology of schizophrenia (for a review, see Arnold (2000)). Some morphometric studies (Pearlson et al., 1997; Turetsky et al., 2003; Baiano et al., 2008) but not all (Kalus et al., 2005) showed volume reductions in the entorhinal cortex in patients with schizophrenia. These volume reductions were not found in those with MDD (Gerritsen et al., 2011), bipolar disorder (Pearlson et al., 1997), or euthymic bipolar disorder (Delaloye et al., 2009). However, the volume of the hippocampal–entorhinal cortex was inversely associated with the number of years since the first lifetime episode of depression (Bell-McGinty et al., 2002). It is interesting that treatment-resistant MDD was also associated with volume reduction of the entorhinal cortex in female patients (Furtado et al., 2008).

Besides serving as an indispensable structural component of neuronal membranes, DHA is known to exert anti-apoptotic effects (Akbar et al., 2005) and to facilitate neuronal growth (Kawakita et al., 2006), dendritic arborization (Calderon and Kim, 2004), and synapse formation (Cao et al., 2009). Conklin et al. (2007) found a positive correlation between intake of *n*−3 PUFAs and volume of the corticolimbic gray matter (amygdala, hippocampus, and anterior cingulate cortex) in 55 healthy adults.

To the best of our knowledge there have been no reports of fatty acid profiles in the entorhinal cortex in individuals with psychiatric disorders to date. In this study, we investigated the levels of PUFAs in the entorhinal cortex of patients with schizophrenia, bipolar disorder, or MDD and compared them with those of unaffected control subjects.

2. Methods

2.1. Postmortem entorhinal cortex samples

Brain tissue samples were obtained from the Stanley Medical Research Institute (SMRI, Rockville, MD). There were 15 patients with each of the following conditions: schizophrenia, bipolar disorder, MDD, and non-pathological conditions. All of them were matched for age, sex, race, postmortem interval, brain pH, and laterality of hemisphere.

The selection, clinical characteristics, diagnosis, and processing of brain tissue have been described previously (Torrey et al., 2000). Briefly, specimens were collected, with informed consent from the patients' next of kin, by participating medical examiners. The specimens were collected, processed, and stored in a standardized manner (Torrey et al., 2000). Diagnoses were made by two senior psychiatrists using DSM-IV criteria and medical records; when necessary, family members were interviewed by telephone. If there is disagreement between them, the records are given to a third senior psychiatrist, and a consensus diagnosis is arrived at. Patients' clinical and demographic characteristics are summarized in Table 1.

Because fatty acid composition is known to vary according to different conditions such as medication (Arvindakshan et al., 2003; Evans et al., 2003; Khan et al., 2002), alcohol drinking (Pawlosky and Salem Jr., 1999), the cause of death including suicide (Huan et al., 2004; Lalovic et al., 2010; Lewis et al., 2011), and relapse vulnerability in substance abusers (Buydens-Branchey et al., 2009), we further analyzed fatty acid composition according to these conditions.

2.2. Tissue preparation and lipid extraction

Frozen sections of entorhinal cortex tissue were scraped off 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. These slides were from the same sets as those used to obtain amygdala tissue in our previous study (Hamazaki et al., 2012). Total lipids were extracted according to the method of 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) 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). Fatty acids were expressed as percentage area of total fatty acids.

2.3. Statistical analysis

Data are expressed as mean ± S.D. 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. We used the Mann–Whitney *U* test with Bonferroni's adjustment for comparison of individual fatty acids between control subjects and patients with each psychiatric disorder. Statistical significance was set at $p < 0.0167$ ($0.05/3 = 0.0167$). In the case of single comparisons for medication, suicide, alcohol abuse, or substance abuse, $p < 0.05$ was considered significant. Data were analyzed with the statistical software SPSS, version 19.0 (IBM Japan, Tokyo).

3. Results

Characteristics of the study participants are shown in Table 1. Matching factors of age, sex, race, postmortem interval, brain pH, and laterality of hemisphere did not differ significantly between the groups. Because brain ischemia is known to result in an increase in free fatty acid (Bazán, 1970), which leads to a decrease of brain pH, it is important to know the brain pH. Patients who more severely abused alcohol were found in all psychiatric groups compared with the control group. There were no suicides in the control group, and chi-square test for suicide rate between the four groups showed a significant difference ($p = 0.003$).

The level of neither DHA (%) nor AA (%) was significantly different between patients with schizophrenia, bipolar disorder, and MDD, and unaffected control subjects (DHA: 11.2 ± 1.5, 11.8 ± 0.9, 11.1 ± 1.4, and 11.9 ± 0.9; AA: 9.1 ± 1.2, 9.7 ± 0.8, 9.7 ± 0.5, and 9.9 ± 0.6, respectively) (Table 2). Significant differences were found

Table 1
Characteristics of patients and control subjects.

	Control $n=15$	Schizophrenia $n=15$	Bipolar disorder $n=15$	Major depressive disorder $n=15$	*p* Value[a]
Age at death (years)	48 ± 11	45 ± 13	42 ± 12	47 ± 9	n.s.
Sex (male/female)	9/6	9/6	9/6	9/6	n.s.
Postmortem interval (h)	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.
No. of suicides	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.
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.

[a] 2 × 4 chi-square test for categorical variables and one-way ANOVA for continuous variables.