Journal of Psychiatric Research 46 (2012) 1024–1028

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

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

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ARTICLE INFO

Article history:
Received 15 February 2012
Received in revised form
9 April 2012
Accepted 11 April 2012

Keywords:
Polyunsaturated fatty acids
Case-control study
Schizophrenia
Bipolar disorder
Major depressive disorder
Postmortem brain

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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doi:10.1016/j.jpsychires.2012.04.012

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.

each psychiatric disorder. Statistical significance was set at $p < 0.0167$ (0.05/3 = 0.0167). In the case of single comparisons, $p < 0.05$ was considered significant. Statview (Japanese version 5; SAS Institute, CA) was used for calculations.

3. Results

The fatty acid composition of the amygdala was generally consistent with the results from our previous study of the hippocampus (Hamazaki et al., 2010), except for DPA (n-6) levels (Table 2). The mean levels of DPA (n-6) in patients were approximately 0.03% in the amygdala, and were not significantly different from that in the controls (0.02%). These values were much lower than those previously observed in the hippocampus (Hamazaki et al., 2010). The percentage of DHA was 10.0 ± 1.1, 10.0 ± 1.3, 9.3 ± 1.3, and 9.7 ± 1.1 in patients with schizophrenia, bipolar disorder, and MDD, and unaffected controls, respectively (not significantly different). The corresponding percentages of AA were 9.0 ± 0.8, 9.2 ± 0.5, 9.4 ± 0.7, and 9.4 ± 0.7, respectively (not significantly different). The corresponding ratios of AA/DHA were 0.92 ± 0.13, 0.93 ± 0.11, 1.03 ± 0.15, and 0.98 ± 0.09, respectively (not significantly different). There were significant differences in some of the other fatty acids. We found a 6.5% increase in palmitic acid ($p = 0.005$) and 6.2% decrease in oleic acid ($p = 0.008$) in MDD patients compared to controls. With regard to schizophrenia, there was an 8.0% decrease in docosatetraenoic acid (22:4n-6) compared to controls ($p = 0.008$).

No significant differences in any fatty acid levels were seen in males ($n = 9$ for each group). In females ($n = 6$ for each group), however, levels of the following fatty acids were significantly different between patients with MDD and the female controls: in MDD patients, palmitic acid levels were significantly higher than in the controls (23.5 ± 1.0% and 21.8 ± 0.7%, respectively, $p = 0.016$), stearic acid levels were significantly higher (26.1 ± 0.9% and 24.8 ± 0.4%, respectively, $p = 0.016$).

When compared between patients not taking antipsychotic medications (total $n = 4$; schizophrenia $n = 1$ and bipolar disorder $n = 3$) and those taking them (total $n = 26$; schizophrenia $n = 14$ and bipolar disorder $n = 12$), DHA levels were significantly higher in the former than the latter (11.2±1.0% and 9.8±1.1%, respectively, p=0.044). No other fatty acids were significantly different between these two groups of patients. Furthermore, the DHA levels in the antipsychotic-free patients were also significantly higher than the controls (11.2±1.0% and 9.7±1.1%, respectively, p=0.028).

Twenty subjects (control $n = 0$, schizophrenia $n = 4$, bipolar disorder $n = 9$, and MDD $n = 7$) died from suicide, and the remaining 40 (control $n = 15$, schizophrenia $n = 11$, bipolar disorder $n = 6$, and MDD $n = 8$) died from other causes. No significant differences in amounts of DHA (9.7 ± 1.3% for suicide deaths and 9.7 ± 1.1% for non-suicide deaths) or AA (9.2 ± 0.7% and 9.4 ± 0.7%, respectively) were observed. Similar results were found for the other PUFAs. Exclusion of the controls did not markedly change the results.

When study subjects were categorized according to alcohol abusers (total $n = 13$; control $n = 0$, schizophrenia $n = 3$, bipolar disorder $n = 6$, and MDD $n = 4$) and non-abusers with levels of alcohol consumption from “none” to “moderate” (total $n = 46$; control $n = 15$, schizophrenia $n = 12$, bipolar disorder $n = 8$, and MDD $n = 11$), no significant differences in DHA levels were observed between the two groups (9.9 ± 1.7% and 9.6 ± 1.7%, respectively). Furthermore, none of the other fatty acids differed significantly between these two groups.

Nine substance abusers (control $n = 0$, schizophrenia $n = 3$, bipolar disorder $n = 3$, and MDD = 3) and 50 non-abusers (control $n = 15$, schizophrenia $n = 12$, bipolar disorder $n = 12$, and MDD $n = 11$) were also compared. No significant differences in the amounts of DHA (10.0 ± 0.9% and 9.6 ± 1.2%, respectively), AA (9.5 ± 0.5% and 9.2 ± 0.5%, respectively), or other fatty acids were observed. Exclusion of the controls did not markedly change these results.

4. Discussion

McNamara et al. determined the total fatty acid composition of post-mortem orbitofrontal cortex from patients with MDD (McNamara et al., 2007a), schizophrenia (McNamara et al., 2007b), and bipolar disorder (McNamara et al., 2008) and found that

Table 2
Fatty acid composition of phospholipids in the post-mortem amygdala of patients with schizophrenia, bipolar disorder and major depressive disorder.

Fatty acids (area %)		Control	Schizophrenia		Bipolar disorder		Major depressive disorder	
		Mean ± SD	Mean ± SD	p value	Mean ± SD	p value	Mean ± SD	p value
Saturated fatty acids								
12: 0	Lauric acid	0.04 ± 0.02	0.05 ± 0.02	0.25	0.05 ± 0.03	0.23	0.06 ± 0.04	0.07
14: 0	Myristic acid	0.38 ± 0.10	0.41 ± 0.05	0.82	0.42 ± 0.06	0.49	0.42 ± 0.06	0.22
16: 0	Palmitic acid	21.69 ± 1.58	22.70 ± 0.93	0.05	22.17 ± 0.97	0.60	23.10 ± 0.97	0.005
18: 0	Stearic acid	25.40 ± 0.98	25.34 ± 0.50	0.63	25.29 ± 0.66	0.98	26.44 ± 2.59	0.05
20: 0	Arachidic acid	0.25 ± 0.10	0.27 ± 0.04	0.06	0.25 ± 0.03	0.11	0.26 ± 0.06	0.22
22: 0	Behenic acid	0.09 ± 0.03	0.10 ± 0.04	0.98	0.09 ± 0.03	0.52	0.09 ± 0.03	0.55
24: 0	Lignoceric acid	0.49 ± 0.12	0.46 ± 0.13	0.31	0.47 ± 0.16	0.47	0.44 ± 0.11	0.18
Monounsaturated fatty acids								
16: 1 n-7	Palmitoleic acid	0.61 ± 0.09	0.67 ± 0.10	0.27	0.65 ± 0.10	0.85	0.60 ± 0.08	0.52
18: 1 n-9	Oleic acid	17.95 ± 0.96	17.42 ± 1.06	0.19	17.62 ± 0.95	0.33	16.83 ± 1.23	0.008
18: 1 n-7	Vaccenic acid	4.49 ± 0.28	4.58 ± 0.40	0.72	4.33 ± 0.28	0.14	4.26 ± 0.28	0.04
20: 1 n-9	Gondoic acid	0.77 ± 0.15	0.73 ± 0.12	0.42	0.73 ± 0.20	0.42	0.65 ± 0.14	0.04
24: 1 n-9	Nervonic acid	1.38 ± 0.51	1.35 ± 0.39	0.98	1.41 ± 0.47	0.98	1.13 ± 0.32	0.08
n-3 polyunsaturated fatty acids								
18: 3 n-3	α-Linolenic acid	0.06 ± 0.02	0.06 ± 0.03	0.69	0.07 ± 0.02	0.22	0.08 ± 0.01	0.019
22: 5 n-3	Docosapentaenoic acid (n-3)	0.09 ± 0.05	0.11 ± 0.07	0.49	0.09 ± 0.06	0.93	0.08 ± 0.07	0.26
22: 6 n-3	Docosahexaenoic acid	9.71 ± 1.13	9.97 ± 1.07	0.25	10.03 ± 1.28	0.37	9.26 ± 1.32	0.18
n-6 polyunsaturated fatty acids								
18: 2 n-6	Linoleic acid	0.53 ± 0.12	0.50 ± 0.10	0.37	0.57 ± 0.22	0.52	0.55 ± 0.11	0.22
20: 3 n-6	Dihomo-γ-Linolenic acid	0.75 ± 0.12	0.87 ± 0.17	0.07	0.79 ± 0.16	0.82	0.76 ± 0.14	0.85
20: 4 n-6	Arachidonic acid	9.44 ± 0.68	9.02 ± 0.76	0.12	9.24 ± 0.49	0.42	9.36 ± 0.73	0.66
22: 4 n-6	Docosatetraenoic acid	5.86 ± 0.44	5.39 ± 0.42	0.008	5.70 ± 0.41	0.49	5.59 ± 0.46	0.19
22: 5 n-6	Docosapentaenoic acid (n-6)	0.02 ± 0.01	0.03 ± 0.02	0.37	0.03 ± 0.02	0.52	0.03 ± 0.02	0.40

p value: Mann–Whitney U test compared to "Control".

amounts of DHA were significantly lower by 22%, 20%, and 24%, respectively, in patients than in controls. In contrast to their findings, in the present study there were no decreases in DHA levels in the post-mortem amygdala from patients with schizophrenia ($n = 15$), MDD ($n = 15$), or bipolar disorder ($n = 15$). These findings suggest that comparatively low DHA values are not a general phenomenon, but might be specific to certain regions of the diseased brain. Changes in other fatty acids found in these psychiatric disorders might also be specific to certain brain regions.

McNamara et al. (2007b) conducted a sub-analysis comparing patients with typical ($n = 9$) or atypical ($n = 9$) antipsychotic medication and without medication ($n = 3$), and controls ($n = 26$). They found that DHA and AA deficits were partially normalized in patients with schizophrenia treated with medication (normalization was higher in the atypical than in the typical treatment group). Our results were inconsistent with their findings. Because their and our sub-analyses were based on small numbers of subjects, this field needs to be further investigated.

We previously conducted a case-control study with 100 suicide attempters and 100 controls, and found an inverse association between the risk of suicide attempt and erythrocyte DHA concentration (Huan et al., 2004). Recently, Lewis et al. (Lewis et al., 2011) conducted a nested case-control study with 800 military personnel who had died from suicide and 800 control personnel, and found that the risk of suicide death was significantly higher in those with low serum DHA levels. In the present study, no significant differences in PUFA levels were found between the suicide ($n = 20$) and non-suicide ($n = 40$) groups. This finding is consistent with previous post-mortem brain studies (Lalovic et al., 2007; McNamara et al., 2009). There are a few possible reasons for the positive results in studies with blood but not those with post-mortem brains (see also the discussion of limitations below). First, PUFA metabolism might be completely different in blood and brain. Second, there were too few study samples from suicide completers for any differences to reach statistical significance. Third, confounding factors such as drugs and diet including alcohol consumption might not have been well adjusted for, especially in postmortem brain studies.

The significant differences in palmitic and oleic acids found in the MDD group (Table 2) might be explained by the decreased expression of genes involved in fatty acid biosynthesis. McNamara and Liu (McNamara and Liu, 2011) conducted a case-control study with postmortem prefrontal cortices and found that Δ5 desaturase mRNA expression was significantly lower in patients with MDD than in controls, and that gene expressions of Δ6 desaturase (D6D), HELO1, and stearoyl-CoA desaturase (SCD) in patients with MDD tended to be lower than in controls. SCD converts 16:0 into 16:1n-7 and 18:0 into 18:1n-9, and its activity can be indicated by the ratios of 16:1n-7/16:0 or 18:1n-9/18:0. In fact, in the present study both ratios were lower in patients with MDD than in controls (16:1n-7/16:0-ratio: 0.026 ± 0.003 and 0.028 ± 0.003, $p = 0.11$ and 18:1n-9/18:0-ratio: 0.64 ± 0.08 and 0.71 ± 0.05, $p = 0.006$ in patients with MDD and controls, respectively). Consequently, gene expressions related to fatty acid desaturation in the amygdala might be similar to those in the orbitofrontal cortex.

Analysis of sex differences showed that significant differences in palmitic and oleic acids in patients with MDD were all derived from females and not from males. Among patients with MDD, there were no significant differences in any fatty acids between sexes except for 20:1n-9 (females: $0.55 \pm 0.16\%$; males: $0.72 \pm 0.06\%$; $p = 0.034$). It is interesting that McNamara et al. (McNamara et al., 2007a) also found sex differences in the orbitofrontal cortex in patients with MDD: female patients exhibited greater DHA deficiency (−32%) than male patients (−16%). Unfortunately this area of research is still at a very early stage and needs further investigation. Significant differences between sexes were not found in any fatty acids among the controls (data not shown).

With regard to schizophrenia, a significant decrease in docosatetraenoic acid (22:4n-6) was observed in comparison to controls (Table 2). AA was lowest in patients with schizophrenia compared to the other three groups, but this difference did not reach significance. In our previous study (Hamazaki et al., 2010) in the hippocampus we also showed a reduction of AA in comparison to controls (schizophrenia, $7.99 \pm 0.79\%$ and control, $8.44 \pm 0.70\%$, $p = 0.02$). In order to maintain appropriate AA concentrations in the amygdala, a considerable amount of 22:4n-6 might be consumed for retroconversion to AA. Liu et al. (Liu et al., 2009) investigated the expression of D6D mRNA in the postmortem prefrontal cortex of patients with schizophrenia and controls, and found that expression was significantly higher in the former. Nevertheless, the 20:4/18:2 ratio (a marker of D6D activity) did not correlate with D6D mRNA expression in patients with schizophrenia, whereas this ratio correlated well in controls, suggesting a potential deficit in D6D enzyme activity in schizophrenia (Liu et al., 2009). In patients with schizophrenia, therefore, 22:4n-6 might be a more important source for AA than in patients with other types of psychiatric disorders.

There were several limitations in the present study. First, the number of subjects in each group was rather small in comparison to our previous study in the hippocampus (control $n = 35$, bipolar disorder $n = 34$, and schizophrenia $n = 35$), although the characteristics were well matched (Table 1). Secondly, there was no information regarding dietary intake of fatty acids, although this limitation is quite common to this area of research with post-mortem brains. Thirdly, no information was available regarding manic and depressive symptoms in patients with bipolar disorder; however, McNamara et al. (McNamara et al., 2010) previously reported that erythrocyte DHA concentration was not significantly correlated with depression or mania symptom severity scores.

In conclusion, we found no marked alteration in the levels of n-3 PUFAs in the amygdala of patients with schizophrenia, bipolar disorder, or MDD. However, palmitic acid was higher and oleic acid was lower in patients with MDD, and docosatetraenoic acid (n-6) was lower in individuals with schizophrenia, suggesting differential fatty acid metabolism in the amygdala of these patients. Further studies are needed to understand the neuropathology of psychiatric disorders.

Role of funding source

This work was supported by the Japan Society for the Promotion of Science, the Ichiro Kanehara Foundation for Promotion of Medical Sciences and Medical Care, and Polyene Project, Inc. The funding sources had no further role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

Kei Hamazaki designed and performed the experiments, and wrote the paper. Tomohito Hamazaki and Hidekuni Inadera wrote the paper.

Conflicts of interest statement

K.H. received research support from the Japan Society for the Promotion of Science, the Tamura Foundation for Promotion of Science and Technology, and the Ichiro Kanehara Foundation for Promotion of Medical Sciences and Medical Care, and consultancy fees from Polyene Project, Inc. and Otsuka Pharmaceutical Co., Ltd., as well as lecture fees and research support from Nippon Suisan

Kaisha, Ltd. T.H. has received research support from the Japan Society for the Promotion of Science, Open Research Center for Lipid Nutrition (Kinjo Gakuin University), and Nippon Suisan Kaisha, Ltd., consultancy fees from Polyene Project, Inc. and Otsuka Pharmaceutical Co., Ltd., and lecture fees from Mochida Pharmaceutical Co., Ltd.

Acknowledgments

We are grateful to Ms. Hiroko Hamatani (University of Toyama), Ms. Shizuko Takebe (University of Toyama), Dr. Kenta Matsumura (School of Mechanical Engineering, College of Science and Engineering, Kanazawa University, Japan) and Dr. Kwang Choi (Department of Psychiatry, Center for the Study of Traumatic Stress, Uniformed Services University of Health Sciences, Bethesda, MD) for technical assistance. We thank Drs. Michael B. Knable, E. Fuller Torrey, Maree J. Webster, Serge Weis, and Robert H. Yolken at the SMRI for donation of brain samples.

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