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Phospholipid Profile in the Postmortem Hippocampus of Patients with Schizophrenia and Bipolar Disorder: No Changes in Docosahexaenoic Acid Species

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Abstract

Previous studies with postmortem brain tissues showed abnormalities not only in n-3 long-chain polyunsaturated fatty acids (PUFA) but also in phospholipid metabolism in the cortex of individuals with schizophrenia and mood disorder. In this study we investigated whether there is similar abnormality in n-3 long-chain PUFAs and/or in phospholipid profile in the hippocampus of schizophrenia and bipolar disorder patients compared to unaffected controls. Using high-performance liquid chromatography/electrospray ionization–mass spectrometry (LC/MS), the phospholipid contents in the postmortem hippocampus from 35 individuals with schizophrenia, 34 individuals with bipolar disorder and 35 controls were evaluated. Unlike the previous findings from orbitofrontal cortex, we found no significant differences in either n-3 long-chain PUFA or total phosphatidylserine (PS), phosphatidylethanolamine (PE) and phosphatidylcholine (PC). However, docosapentaenoic acid (n-6, 22:5n-6)-PS and 22:5n-6-PC were significantly lower in individuals with schizophrenia or bipolar disorder than the controls. When fatty acid contents were estimated from PS, PE and PC, 22:5 n-6 was significantly lower in both patient groups compared to the controls. From these results we concluded that DHA loss associated with these psychiatric disorders may be specific to certain regions of the brain. The selective decrease in 22:5n-6 without affecting DHA contents suggests altered lipid metabolism, particularly n-6 PUFA rather than n-3 PUFA, in the hippocampus of individuals with schizophrenia or bipolar disorder.

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Contributors

Kei Hamazaki performed the experiments and data analysis and wrote the paper.

Kwang H Choi performed data analysis

Hee-Yong Kim conceived and designed the study, performed data analysis, and wrote the paper.

INTRODUCTION

Since Horrobin (1977) hypothesized that schizophrenia might be a prostaglandin deficiency disease, several studies have reported various changes in PUFA levels in brains (Horrobin et al., 1991; McNamara et al., 2007a), plasma (Bates et al., 1991; Kaiya et al., 1991; Kale et al., 2008) and red blood cell (RBC) membranes (Kale et al., 2008; Assies et al., 2001; Khan et al., 2002; Arvindakshan et al., 2003; Peet et al., 2004) of patients with schizophrenia. Recently McNamara et al. (2007a) determined the total fatty acid composition of postmortem orbitofrontal cortex from patients with schizophrenia and age-matched normal controls, and found that, after correction for multiple comparisons, DHA was significantly lower by 20% in the patients with schizophrenia than in normal controls. However, a meta-analysis of clinical trials administering omega-3 PUFAs to patients with schizophrenia did not show any significant improvement (Freeman et al., 2006).

The same phenomenon was seen in mood disorders. Noaghiul et al. (2003) examined the epidemiological data on lifetime prevalence rates for bipolar disorder by cross-national comparisons and found that robust correlational relationship between greater seafood consumption and lower prevalence rates of bipolar disorder. McNamara et al. (2007b) investigated the fatty acids from postmortem orbitofrontal cortex of patients with major depressive disorder (n = 15) and age-matched normal controls (n = 27), and found that DHA was the only fatty acid that was significantly different (–22%) from the controls. Moreover, a meta-analysis of clinical trials of omega-3 PUFAs in bipolar disorder and major depression patients showed a significant improvement (Freeman et al., 2006).

Several reports have addressed the involvement of the prefrontal cortex in the pathophysiology of schizophrenia and bipolar disorder, whereas less attention has been given to the role of the hippocampus. Goldberg et al. (1994) conducted a study with monozygotic twin pairs discordant for schizophrenia and found the correlation between hippocampal volume and impaired verbal memory. Anatomical structures of the hippocampus revealed that the size was significantly decreased in comparison to that of controls (Harrison et al., 2004; Pearson and Marsh, 1999; Shenton et al., 2001). The size of hippocampal pyramidal neurons was also found to be smaller in patients with schizophrenia (Jonsson et al., 1999; Zaidel et al., 1997). Moreover, Kolmeets et al. (2005) investigated the mossy fiber synapses in the CA3 hippocampal region in the postmortem brains of schizophrenia and normal controls, and found that the volume and total number of spines were significantly reduced compared with the control group.

The etiology of bipolar disorder is still unclear, however an emerging body of evidence suggests that impairment of the hippocampus could be one of the mechanisms of the development of this disease (Brown et al., 1999). Several investigators reported that there was an impairment of cognitive function in patients with bipolar disorder (McKay et al., 1995; Coffman et al., 1990; Sapin et al., 1987). Moorhead et al. (2007) conducted a prospective cohort study of individuals with bipolar disorder and found that the patients showed a larger decline in the hippocampal volume over 4 years than control subjects, and this tissue loss was associated with deterioration in cognitive function and the course of illness. Monozygotic twin studies revealed that the right hippocampus was smaller in affected bipolar twins than well ones (Noga et al., 2001). Moreover, they found abnormalities in verbal memory measures in the affected bipolar twins relative to the unaffected co-twins (and the normal twins) (Gourovitch et al., 1999). Taken together, these results suggest that the abnormalities of hippocampal region may have contributed to this disorder.

Up to date, there are no data regarding the phospholipid and fatty acid profiles in the hippocampus of individuals with schizophrenia and with bipolar disorder. In this study, we tested whether hippocampal phospholipid levels, particularly n-3 long-chain polyunsaturates,

are different between schizophrenic or bipolar patients and the normal controls. Since both bipolar disorder and schizophrenia share many common features [clinical symptoms (American Psychiatric Association 1994; World Health Organization, 2005) heredity (Gershon et al., 1988; Angst et al., 1980), molecular genetics (Berrettini et al., 2001), neuro-developmental etiological processes (Nasrallah, 1991), etiologic risk factors (Torrey, 1999), neuroanatomy, neurobiology (Laruelle et al., 1999) and medication (Glick et al., 2001)], we included both schizophrenia and bipolar disorder subjects. We found no changes in n-3 polyunsaturates in the hippocampal phospholipids. Instead, we found that the hippocampus of schizophrenia and bipolar patients contained significantly lower docosapentaenoic acid (22:5n-6, DPA_n-6) in PS and PC, suggesting abnormal metabolism of long chain n-6 PUFA species in both psychiatric disorders.

METHODS

Postmortem hippocampal tissues

Brain tissues were obtained from the Stanley Medical Research Institute (SMRI). There were 35 schizophrenia, 35 bipolar disorder and 35 control individuals (Array Collection) that were matched in age and sex. These specimens were collected, with informed consent from next-of-kin, by participating medical examiners between 1995 and 2005. The specimens were collected, processed, and stored in a standardized way (Torrey et al., 2000). Exclusion criteria for the specimens included 1) significant structural brain pathology on postmortem examination by a qualified neuropathologist or by premortem imaging, 2) history of significant focal neurological signs, 3) history of central nervous system disease that could be expected to alter gene expression in a persistent way, 4) documented IQ < 70, 5) poor RNA quality (vide infra). Additional exclusion criteria for unaffected controls were: 6) age less than 30 (thus, still in the period of maximum risk), 7) substance abuse within one year of death or evidence of significant alcohol-related changes in the liver.

Diagnoses were made by two senior psychiatrists, using DSM-IV criteria and based on medical records and, when necessary, telephone interviews with family members. Diagnosis of unaffected controls was based on structured interviews by a senior psychiatrist with family member(s) to rule out Axis I diagnosis (Torrey et al., 2000). After the data were submitted to the SMRI, diagnostic status and a range of clinical variables were provided for analysis from the SMRI. Their demographic characteristics are summarized in Table 1. One subject from bipolar disorder group was removed from analysis because the subject had a cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Tissue preparation and lipid extraction

Hippocampal tissues were scraped off from 3 consecutive frozen sections from the slides (14µm each) and homogenized in ice-cold HEPES buffer (pH 7.4), and aliquots were subjected to protein assay and lipid analysis. Total lipids were extracted according to the method of Bligh and Dyer (Bligh and Dyer, 1959).

Phospholipid analysis

Phospholipid molecular species were separated and analyzed using reversed-phase HPLC/ESI-MS with a C18 column (Prodigy, 150 × 2.0 mm, µm; Phenomenex, Torrance, CA, USA) as described previously (Kim et al., 1994). The separation was accomplished using a linear solvent gradient (water:0.5% ammonium hydroxide in methanol:hexane), changing from 12:88:0 to 0:88:12 in 17 min after holding the initial solvent composition for 3 min at a flow rate of 0.4 mL/min (Ma and Kim, 1995). An Agilent 1100 LC/MSD instrument (Palo Alto, CA, USA) was used to detect the separated phospholipid molecular species. For electrospray ionization, the drying gas temperature was 350°C; the drying gas flow rate and nebulizing gas

pressure were 11 L/min and 45 p.s.i., respectively. The capillary and fragmentor voltages were set at 4500 and 300 V, respectively. Identification of individual phospholipid molecular species was based on the monoglyceride, diglyceride and protonated molecular ion peaks (Kim et al., 1994). As internal standards representing three phospholipid classes, we used 1-d35-stearoyl-2-docosapentanoyle-glycerophosphoserine (d3518:0,22:5-PS), 1-d35-stearoyl-2-arachidonoyl-glycerophosphoethanolamine (d3518:0,20:4-PE) and 1-d35-stearoyl-2-linoleoyl-glycerophosphocholine (d3518:0,18:2-PC). Quantitation of phospholipid species was based on the area ratio calculated against the added deuterium-labeled internal standards using diglyceride ions for PS and PE, and protonated molecular ions for PC. They were standardized with protein content which was measured spectrophotometrically using bicinchoninic acid as the reaction reagent as described earlier (Smith et al., 1985).

Fatty acids analysis

The total amount of each fatty acid was calculated as a sum of concentrations in PS, PE and PC. The individual fatty acid distribution is expressed as the % of the sum of all fatty acids.

Statistical analysis

Data are expressed as means $\pm$ SD. Statistical difference between the psychiatric disorder group and the control group was assessed using an unpaired Student's t-test. $p < 0.05$ was considered to be significant.

RESULTS

The amounts of PS, PE and PC in the hippocampus assessed by HPLC/EIS-MS are shown in Fig 1. There were no significant differences between groups in the total amounts of any PL species. This was also the case for sum of PS, PE and PC (526 ± 52 , 521 ± 46 and 520 ± 68 pmol/ μ g protein in control, schizophrenia and bipolar disorder, respectively). PC was the highest followed by PE and PS species, which was consistent with a previous report using rats (Wen and Kim, 2004). The phospholipid containing 18:0,18:1 was the most abundant in PS species followed by 18:0,22:6 (Fig 2-a); 18:0,20:4 was the most abundant in PE species followed by 18:0,22:6 (Fig 2-b), and 16:0,18:1 was the most abundant in PC followed by 18:0,18:1 (Fig 2-c), which was almost identical to our previous report from rat hippocampus (Wen and Kim, 2004).

For PS molecular species (Fig 2-a), 18:0,18:1 levels in the schizophrenia group (+12.2%) were significantly higher than the control group. 18:0,22:5n-6 levels of the bipolar disorder and schizophrenia groups were significantly lower than the controls (-13.4 %, and -19.5%, respectively). There were no significant differences in any individual molecular species of PE (Fig 2-b). Among PC molecular species (Fig 2-c), n-6 PUFA-containing species such as 16:0,20:4, 16:0,22:5 and 18:0,22:5 were significantly lower in the schizophrenia group than in the control group (-7.5 %, -14.9% and -18.6%, respectively). As for bipolar disorder (Fig 2-c), 18:0,22:5n-6 was significantly lower than the controls (-20.7%), and there was a tendency for 16:0,22:5n-6 to be lower than the controls (-13.5%) although statistical significance was not met for this species.

When the fatty acid levels were estimated from all phospholipids determined, arachidonic acid (AA, 20:4n-6) and 22:5n-6 in the schizophrenia group were significantly lower than the control group (-5.3 % and -10.6 %, respectively) (Fig 3). As for bipolar disorder, only 22:5n-6 was significantly lower than the controls (-7.5%). This was also the case within individual phospholipid classes. The 22:5n-6 levels in PS in both schizophrenia and bipolar disorder groups were significantly decreased (-16.6% $p=0.002$, -19.2% $p=0.0004$, respectively). Despite no significant differences found in PE molecular species, a slight but significant

decrease of 22:5n-6 was observed when evaluated for the fatty acid content in schizophrenia (−7.9% $p=0.04$). The 22:5n-6 levels in PC in both schizophrenia and bipolar disorder groups (−8.6% $p=0.02$, −7.8% $p=0.04$, respectively) and the AA level in the bipolar disorder group (−2.0% $p=0.03$) were significantly decreased compared with the controls.

DISCUSSION

Unlike the previous findings from the orbitofrontal cortex (McNamara et al. 2007a, 2007b), no decrease in the DHA content was observed in the postmortem hippocampus from a relatively large number of patients with schizophrenia ($n=35$) or bipolar patients ($n=34$). These findings indicate that DHA loss may not be a general phenomenon, but specific to certain regions of the diseased brain. Accordingly, DHA supplementation or its deficiency may exert differential effects on orbitofrontal cortex- and hippocampus-related functions. We also found that 22:5n-6-containing PS and PC were selectively decreased in the postmortem hippocampus of both schizophrenia and bipolar disorder patients. It is well documented that a decreased amount of DHA in brain membrane phospholipids, secondary to inadequate dietary n-3 PUFA intake, results in a reciprocal increase in DPAn-6 in brains (Hrboticky et al., 1990; Innis, 1991; Neuringer et al., 1986). However, the decrease of DPAn-6 without altering the DHA level has not been demonstrated before. Our findings on the loss of DPAn-6, particularly in specific phospholipid classes, suggest an involvement of this fatty acid and related metabolism in the neuropathology of schizophrenia or bipolar disorder, although the mechanism for this decreased is unclear.

Increased glutamate concentrations have been reported in the hippocampus in magnetic resonance spectroscopy (MRS) studies of individuals with bipolar disorder (Colla et al., 2009) and schizophrenia (van Elst et al., 2005), although the latter finding was controversial (Theberge et al., 2006). Stimulation of NMDA receptors by glutamate can activate Ca^{2+} -dependent cytosolic phospholipase A2 α (cPLA2 α) and release AA (Dumuis et al., 1988). In order to maintain appropriate AA levels in the hippocampus, conversion and retroconversion to AA from 18:2n-6 and 22:5n-6, respectively, are two possible pathways for AA accumulation. As the 18:2n-6 content in the brain is minimal, 22:5n-6 might be the major source for producing AA in patients with schizophrenia and bipolar disorders. Liu et al. (2009) investigated expression of $\Delta 6$ desaturase mRNA in the postmortem prefrontal cortex of patients with schizophrenia and controls and found that $\Delta 6$ desaturase expression was significantly higher in the former. Nevertheless, the 20:4/18:2 ratio did not correlate with $\Delta 6$ desaturase mRNA expression in schizophrenic patients, while those parameters correlated well in controls, suggesting a potential deficit in $\Delta 6$ desaturase enzyme activity in schizophrenia (Liu et al., 2009).

The decrease of 22:5n-6 in schizophrenia (−10.6%) was greater than that in bipolar disorder (−7.5%) compared to the control group. Moreover, the decrease of AA in schizophrenia (−5.3%) was also greater than that in bipolar disorder (−2.9%). Possible explanation for this observation might be due to different medication regimen. Mood stabilizer drugs, such as lithium, carbamazepine and valproate are known to decrease the AA turnover in rat brain phospholipids (Chang et al., 1996, 2001; Bazinet et al., 2006). Consistently, the levels of 22:5n-6 and AA in the bipolar patients with medication history were found to be close to the control level. When 22:5n-6 and AA in fatty acid levels were compared between bipolar disorder patients with and without medication, 22:5n-6 ($p=0.03$) and AA ($p=0.056$) were higher in the former ($n=9$) than the latter ($n=25$).

Several analyses with phosphorus magnetic resonance spectroscopy (^{31}P MRS) in individuals with schizophrenia and bipolar disorder have been reported (Soares et al., 1996). Those analyses can provide important information about the levels of phosphomonoesters (PMEs),

phosphoethanolamine and phosphocholine, reflecting the metabolic precursors of PL, and also phosphodiester (PDEs), glycerophosphoethanolamine and glycerophosphocholine, reflecting PL degradation products. In general, PME was decreased and PDE was increased in treatment-naïve first episode and chronic schizophrenia subjects (Reddy and Keshavan, 2003), as well as in bipolar disorder subjects (Stork and Renshaw, 2005). However, we did not observe any significant changes in total PS, PE and PC (Fig 1). Although many confounding factors may have affected disease effects on phospholipid profiles, an explanation could be due to the fact that different parts of the brain were analyzed. Most of the ^{31}P MRS studies focused on either the temporal or frontal lobes, not the hippocampus. Jensen et al. (2004) conducted a ^{31}P MRS study in 15 patients with first-episode schizophrenia and 15 healthy volunteers and found no significant differences in PMEs and PDEs in several parts of brain including the hippocampus except the anterior cingulate. These data suggested that membrane PL biosynthesis and degradation, and thus the PL content, may not be altered in these patients' hippocampi as observed in our present study. Nevertheless, detailed PL molecular species analysis revealed slight but significant changes of 22:5n-6 containing PL species, particularly in PS and PC, suggesting a unique metabolic alteration associated with schizophrenia and bipolar disorder.

Komoroski et al. (2008) determined absolute concentrations of the individual PL metabolites of postmortem brains of normal controls and patients with mental illnesses including schizophrenia, and found that glycerophosphocholine was significantly elevated in male schizophrenia patients, but no changes in glycerophosphoethanolamine, suggesting that PC was more degradable than PE. These findings are consistent with our observation that some changes were detected in individual PC molecular species but not in PEs (Fig 2).

In schizophrenia the left hippocampus seemed to be larger than the right (Harrison, 2004). However, a study with monozygotic twins discordant for bipolar disorder, revealed that the right hippocampus was smaller in the affected vs. well twins (Noga et al., 2001). In the present study, we did not find any significant differences in total PS, PE and PC or fatty acids between the left and right sides of the hippocampus in schizophrenia ($n=17$ vs $n=18$, respectively), and in bipolar disorder ($n=19$ vs $n=15$, respectively) (data not shown). This was also the case when both disease groups were combined as "left hippocampus ($n=52$)" vs "right hippocampus ($n=52$)" (data not shown).

In conclusion, we found no marked alteration of n-3 long chain PUFA in the hippocampus of patients with schizophrenia or bipolar disorder. However, 22:5 n-6-containing PL species, particularly in PS and PC, were lower in individuals with schizophrenia or with bipolar disorder, suggesting differential PL metabolism in the hippocampus of these patients, thus remaining an area of investigative interest in the neuropathology of psychiatric disorders.

Abbreviations

PC	phosphatidylcholine
PL	phospholipid
PE	phosphatidylethanolamine
PS	phosphatidylserine
PUFAs	polyunsaturated fatty acids
AA	arachidonic acid
DHA	docosahexaenoic acid

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Figure 1.

The total phosphatidylserine, phosphatidylethanolamine and phosphatidylcholine of the postmortem hippocampus of controls (n=35), schizophrenic (n=35) and bipolar patients (n=34). Values shown as mean with SD.

Figure 2.

The content of individual Phosphatidylserine (Figure 2-a), Phosphatidylethanolamine (Figure 2-b) and Phosphatidylcholine (Figure 2-c) molecular species in hippocampi of the postmortem hippocampus of controls (n=35), schizophrenic (n=35) and bipolar patients (n=34). * $p < 0.05$, ** $p < 0.001$ versus control.

Figure 3.

The fatty acids were summed from individual phospholipid species of PS, PE and PC of hippocampi of controls (n=35), schizophrenic (n=35) and bipolar patients (n=34). * $p < 0.05$, ** $p < 0.005$ versus control.

Table 1

Subject characteristics

Comparison of subject and brain tissue characteristics	Control (n = 35)	Schizophrenia (n = 35)	Bipolar (n = 34)
Age (mean hours $\pm$ S.D.)	44.2 $\pm$ 7.6	42.6 $\pm$ 8.5	45.4 $\pm$ 10.7
Postmortem interval (mean hours $\pm$ S.D.)	29.4 $\pm$ 12.9	31.4 $\pm$ 15.5	37.9 $\pm$ 18.6
Brain tissue pH (mean $\pm$ S.D.)	6.61 $\pm$ 0.27	6.47 $\pm$ 0.24	6.43 $\pm$ 0.30
Cause of death			
Suicide	0	7	15
Cardiopulmonary	34	21	10
Accident	0	1	3
Other	1	6	6
Gender male / female	26 / 9	26 / 9	16 / 18

Values are means $\pm$ SD.