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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 form 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, 22:5n-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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1. 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 and Hibbeln (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

Abbreviations: PC, phosphatidylcholine; PL, phospholipid; PE, phosphatidylethanolamine; PS, phosphatidylserine; PUFAs, polyunsaturated fatty acids; AA, arachidonic acid; DHA, docosahexaenoic acid.

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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, 2004; Pearlson 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, Kolomeets 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, 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, DPAn-6) in PS and PC, suggesting abnormal metabolism of long chain n-6 PUFA species in both psychiatric disorders.

2. Methods

2.1. 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.

2.2. Tissue preparation and lipid extraction

Hippocampal tissues were scraped off from 3 consecutive frozen sections from the slides (14 μm 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 (1959).

2.3. Phospholipid analysis

Phospholipid molecular species were separated and analyzed using reversed-phase HPLC/ESI–MS with a C18 column (Prodigy, 150 × 2.0 mm, 5 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 neublizing gas pressure were 11 L/min and 45 psi, 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-docosapentanoyl-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). Quantita-

Table 1
Subject characteristics.

Comparison of subject and brain tissue characteristics	Control ($n = 35$)	Schizophrenia ($n = 35$)	Bipolar ($n = 34$)
Age (mean hours ± S.D.)	44.2 ± 7.6	42.6 ± 8.5	45.4 ± 10.7
Postmortem interval (mean hours ± S.D.)	29.4 ± 12.9	31.4 ± 15.5	37.9 ± 18.6
Brain tissue pH (mean ± S.D.)	6.61 ± 0.27	6.47 ± 0.24	6.43 ± 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 ± S.D.

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