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Levels of lysophosphatidic acid in cerebrospinal fluid and plasma of patients with schizophrenia

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ABSTRACT

It is suggested that lysophosphatidic acid (LPA) plays a key role in the pathophysiology of schizophrenia. In this study, we measured LPA levels by enzyme-linked immunosorbent assay in cerebrospinal fluid (CSF) and plasma samples. The participants were 49 patients with schizophrenia and 49 normal healthy controls for CSF study, and 42 patients and 44 controls for plasma study. We found that LPA levels in the patients were not significantly different from those of controls in CSF (controls: 0.189 ± 0.077 μM, patients: 0.175 ± 0.067 μM; $P = 0.318$) and plasma samples (controls: 0.131 ± 0.067 μM, patients: 0.120 ± 0.075 μM; $P = 0.465$). On the other hand, CSF levels in medicated patients (0.162 ± 0.061 μM) were significantly lower than those observed in unmedicated patients (0.224 ± 0.067 μM, $P = 0.038$), suggesting that our findings could be masked by the influence of medication with antipsychotics. Interestingly, we detected significant negative correlation between PANSS scores and plasma LPA levels, especially in males and in unmedicated patients. Our result suggests that LPA levels in CSF and plasma samples would not serve as a diagnostic biomarker, but plasma levels could be used for symptomatic assessment of schizophrenia.

1. Introduction

Current diagnostic systems for schizophrenia rely upon presentation of signs and symptoms, and do not adequately reflect relevant disease pathology (Cuthbert and Insel, 2013). Thus, there is an urgent need to develop biomarkers that allow diagnosis of schizophrenia based on its pathophysiology.

Growing evidence suggests that lysophosphatidic acid (LPA; 1-acyl-2-sn-glycerol-3-phosphoate) plays a key role in the central nervous system (Estivill-Torrús. et al., 2013). LPA is a potent bioactive lipid mediator with diverse biological properties (Choi et al., 2010). Previously, intracerebroventricular injection of LPA induced emotional changes in rats (Castilla-Ortega et al., 2014) and mice (Yamada et al., 2015). LPA mainly acts by binding to specific G-protein-coupled seven transmembrane receptors (LPA1–7) in multiple cell types of the nervous system (Frisca et al., 2012). Among them, LPA1 is a Gi-coupled receptor with high affinity for LPA. LPA1 was originally identified in immortalized cortical neuroblasts, and subsequently shown to have a temporally and spatially restricted expression pattern in the developing and adult brain (Hecht et al., 1996; An et al., 1997). Previously, Harrison et al., reported a detailed neurological and behavioral analysis of mice homozygous for targeted deletion of the *LPA1* locus, and suggested that loss of the LPA1 receptor generates defects resembling those found in psychiatric disease (Harrison et al., 2003). Specifically, they observed a marked deficit in prepulse inhibition, widespread changes in levels and turnover of the neurotransmitter serotonin, brain region-specific alterations in levels of amino acids, and craniofacial dysmorphism in these mice. In addition, they demonstrated that the LPA1 mutation produces a number of changes in neurotransmitters previously associated with a schizophrenic-like pathology (Roberts et al., 2005). Furthermore, aberrant LPA receptor signaling was recently associated with fetal brain hemorrhage, which may contribute to

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development of certain neuropsychiatric disorders, as LPA signaling initiates schizophrenia-like brain and behavioral changes in a mouse model of prenatal brain hemorrhage (Mirendil et al., 2015). Altogether, these findings suggest that LPA plays important roles in the development of central nervous system and possibly in the pathophysiology of schizophrenia.

Interestingly, dysregulation in synaptic LPA signaling was shown to cause cortical hyper-excitability in adult mice (Vogt et al., 2016). More recently, it is reported that pharmacological and genetic inhibition of LPA-synthesizing enzyme autotaxin rescued schizophrenia-related cortical hyper-excitability syndromes in mice (Thalman et al., 2018). These results suggest that synaptic LPA levels could also be elevated in the brain of patients with schizophrenia. Therefore, in the present study, we tested the hypothesis that LPA levels in cerebrospinal fluid (CSF) are elevated in patients with schizophrenia.

On the other hand, it is reported that LPA levels in CSF (Jiang et al., 2018) and plasma (Balood et al., 2014; Jiang et al., 2018) are elevated in patients with multiple sclerosis. It is proposed that the LPA levels in CSF and plasma could be used as biomarkers to monitor disease activity and therapeutic responses in the patients. However, LPA levels not only in CSF, but also in plasma samples, are not evaluated in the patients with psychiatric disorders, including schizophrenia. Therefore, we also examined LPA levels in plasma samples of the patients with schizophrenia and compared with normal healthy controls.

2. Methods

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan. Written informed consent was obtained from all participants.

2.1. Participants

Patients were recruited from the NCNP Hospital, Tokyo, Japan. Control subjects were recruited from the community by advertisements in a free local magazine and the NCNP biobank website. Consensus diagnoses were in accordance with Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria (American Psychiatric Association, 1995) on the basis of the Mini-International Neuropsychiatric Interview (MINI), Japanese version (Otsubo et al., 2005; Sheehan et al., 1998) (administered by trained psychologists or psychiatrists), additional unstructured interviews, and information from medical records. Participants were excluded if they had a history of central nervous system disease, severe head injury, or substance abuse. Symptoms of schizophrenia were assessed using the Japanese version of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987; Yamada et al., 1991), which has good inter-rater reliability (Igarashi et al., 1998). Doses of antipsychotics were converted to chlorpromazine equivalent doses using published guidelines (Inada and Inagaki, 2015).

2.2. Lumbar puncture and venipuncture

Lumbar puncture was performed with the subject in the left decubitus position (Hattori et al., 2015). CSF was withdrawn from the L3–L4 or L4–L5 interspace. After removal of 2 ml CSF, a further 10 ml was collected and immediately transferred on ice to be centrifuged at 4 °C and aliquoted for storage at −80 °C until assay. Simultaneously, blood samples were collected by venipuncture and plasma samples obtained by centrifugation.

2.3. Measurement of LPA levels

Enzyme-linked immunosorbent assay (ELISA) was used to quantify LPA levels. LPA Assay Kit II (K-2800S) was purchased from Echelon Biosciences (Salt Lake City, UT, USA). Experiments were performed using 6 μl CSF and 6 μl plasma, according to standard protocols. Intra-assay coefficient of variation (CV) and inter-assay CV of this assay kit are 6.5–8.7% and 8.9–15.33%, respectively. Estimation of LPA concentration in samples was performed according to standard protocols using a calibration curve with GraphPad Prism 7.03 (GraphPad Software Inc., La Jolla, CA, USA).

2.4. Statistical analysis

Statistical differences between groups were calculated by one-way analysis of variance (ANOVA) with post-hoc Tukey–Kramer honest significant difference (HSD) test. The statistical significance of differences between two groups was assessed by Student's *t*-test. The relationships between LPA levels and BMI and age were analyzed by Pearson's correlation test. The relationships between CSF LPA levels and LPA levels in plasma samples was also analyzed by Pearson's correlation coefficient. The relationships between LPA levels and PANSS scores were assessed by Spearman's rank correlation coefficient. Statistical analyses were performed using JMP 12.0 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-tailed, with $P < 0.05$ indicating statistical significance.

3. Results

The participants for CSF study were 49 patients with schizophrenia and 49 normal healthy controls. Demographics of the participants are summarized in Table 1. All healthy controls and 10 patients with schizophrenia were untreated with psychotropic drugs. There were no significant differences in sex ratio, age distribution, body mass, the times of sampling, or the storage times among groups. On the other hand, body mass index (BMI) was significantly higher in the patients ($P = 0.019$).

The participants for plasma study were 42 patients with schizophrenia and 44 normal healthy controls. Demographics of the participants are summarized in Table 1. All healthy controls and 5 patients with schizophrenia were untreated with psychotropic drugs. There were no significant differences in sex ratio, age distribution, body mass, BMI, the times of sampling, or the storage times among groups.

In this study, we found that LPA levels of the females were not significantly different from that of the males in CSF (females: 0.182 ± 0.067 μM, males: 0.182 ± 0.078 μM; $P = 0.997$) and plasma samples (females: 0.135 ± 0.074 μM, males: 0.115 ± 0.067 μM; $P = 0.202$). On the other hand, a significant negative correlation was demonstrated between LPA levels in CSF and age of participants ($F_{1,96} = 4.747$, $P = 0.032$, $r = -0.212$). No correlation was found between LPA levels in plasma samples and age of participants ($F_{1,84} = 0.036$, $P = 0.850$, $r < -0.021$). The correlation between LPA levels and BMI of participants was not observed in both CSF ($F_{1,94} = 2.642$, $P = 0.108$, $r = -0.166$) and plasma samples ($F_{1,80} = 0.007$, $P = 0.933$, $r < -0.009$).

We found that LPA levels in CSF of schizophrenia patients were not significantly different from those of controls in CSF (controls: 0.189 ± 0.077 μM, patients: 0.175 ± 0.067 μM; $P = 0.318$) (Fig. 1). We also found that LPA levels in plasma samples of schizophrenia patients were not significantly different from those of controls (controls: 0.131 ± 0.067 μM, patients: 0.120 ± 0.075 μM; $P = 0.465$) (Fig. 2).

One-way ANOVA demonstrated that LPA levels in CSF were significantly different between the three medication groups ($F_{2,95} = 3.647$, $P = 0.030$). LPA levels in CSF of medicated patients (0.162 ± 0.061 μM) were significantly lower than those of unmedicated patients (0.224 ± 0.067 μM; $P = 0.038$ Tukey–Kramer HSD test) but not different from those of controls (0.189 ± 0.077 μM; $P = 0.171$ Tukey–Kramer HSD test). In contrast, one-way ANOVA demonstrated that LPA levels in plasma samples were not significantly different between the groups (controls: 0.131 ± 0.067 μM, medicated:

Table 1
Demographics of participants.

	CSF			Plasma		
	NC	SZ	*P*	NC	SZ	*P*
N	49	49		44	42	
male (*N*)	25	24		19	23	
unmedicated patients (*N*)		10			5	
age (year)	41.5 ± 11.6	39.7 ± 10.5	0.416	40.7 ± 9.4	40.7 ± 8.9	0.992
body mass (kg)	62.0 ± 14.3	67.9 ± 17.9	0.070	63.5 ± 16.4	65.0 ± 16.8	0.641
BMI	22.5 ± 3.8	25.3 ± 7.3	0.019	23.1 ± 4.2	23.6 ± 4.9	0.528
sampling time (h:m)	12:34 ± 1:58	13:02 ± 1:50	0.216	13:22 ± 1:54	12:39 ± 1:52	0.056
fasting time (min)	211.8 ± 260.0	140.7 ± 126.1	0.125	242.9 ± 248.7	251.9 ± 246.9	0.868
storage time (year)	3.9 ± 1.0	4.0 ± 1.0	0.421	2.6 ± 0.8	2.9 ± 0.9	0.101
PANSS score						
positive symptoms		14.9 ± 5.4			16.7 ± 6.8	
negative symptoms		17.7 ± 5.9			20.2 ± 5.9	
general symptoms		32.3 ± 7.5			36.2 ± 10.9	
total score		65.0 ± 13.7			73.1 ± 20.4	

Values are shown as mean ± standard deviation. NC: normal healthy control, SZ: schizophrenia, PANSS: Positive and Negative Syndrome Scale. The statistical significance of differences was assessed by Student's *t*-test.

0.124 ± 0.078 μM, unmedicated: 0.091 ± 0.039 μM; $F_{2,83} = 0.745$, $P = 0.478$).

Tables 2 and 3 demonstrate the relationships between LPA levels and the PANSS scores. The PANSS assessments were done basically on the same day of the lumbar puncture and/or venipuncture in the patients (72% in CSF study and 87% in plasma study). Average time interval between sample collection and the PANSS assessments were 3.80 ± 8.79 days and 1.17 ± 4.04 days in patients for CSF study and plasma study, respectively. In this study, a significant correlation was not demonstrated between CSF LPA levels and scores for positive syndrome scale ($P = 0.812$, $r = 0.051$), negative syndrome scale ($P = 0.934$, $r = -0.031$), general psychopathology scale ($P = 0.205$, $r = 0.172$), and total scale ($P = 0.458$, $r = 0.067$) (Table 2). On the other hand, a significant negative correlation was demonstrated between plasma LPA levels and scores for positive syndrome scale ($P = 0.034$, $r = -0.321$), general psychopathology scale ($P = 0.020$, $r = -0.313$), and total scale ($P = 0.033$, $r = -0.352$), but not for negative syndrome scale ($P = 0.596$, $r = 0.200$) (Table 3). These correlations were evident in males, but not observed in females. In addition, these correlations were also evident in unmedicated patients but not found in medicated patients (Table 3).

In this study, CSF and plasma samples were collected simultaneously from 21 patients with schizophrenia and 20 healthy controls. Correlation analysis with these 41 samples demonstrated no correlation between CSF LPA levels and LPA levels in plasma samples ($F_{1,39} = 0.252$, $P = 0.619$, $r = 0.080$).

4. Discussion

This is the first report to quantify LPA levels in CSF and plasma samples from patients with schizophrenia. In this study, LPA levels in plasma samples were higher in females than in males, although the difference did not achieve statistical significance. These results are similar to those observed in previous reports (Baker et al., 2001; Hosogaya et al., 2008; Michalczyk et al., 2017), in which higher concentrations of plasma LPA were observed in females, while no sex difference was reported by the other group (Yao et al., 2014). Further studies are needed to explain the sex difference in plasma LPA levels.

In this study, a significant negative correlation was demonstrated between LPA levels in CSF and age of participants. No correlation was found between LPA levels in plasma samples and age of participants. Our results in plasma samples are consistent with a previous report (Yao et al., 2014). However, the influence of age on plasma LPA levels is controversial, since Michalczyk et al. reported positive correlation between age and plasma LPA levels (Michalczyk et al., 2017), and Hosogaya et al. reported negative correlation in females (Hosogaya et al., 2008).

On the other hand, it is recently reported that plasma LPA levels positively correlates with BMI (Michalczyk et al., 2017). However, the correlation between LPA levels and BMI of participants was also not observed in CSF and plasma samples in the present study. Further studies are necessary to clarify these possible correlations.

In the present study, we tested the hypothesis that LPA levels in CSF are elevated in patients with schizophrenia. Unexpectedly, we found

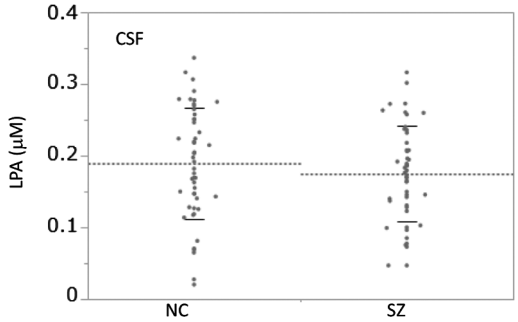

Fig. 1. Lysophosphatidic acid (LPA) levels in cerebrospinal fluid. LPA levels (μM) were measured by enzyme-linked immunosorbent assay in 49 patients with schizophrenia (SZ) and 49 normal healthy controls (NC). Data are expressed as mean ± standard deviation. No significant differences between two groups was observed (Student's *t*-test. $P = 0.318$).

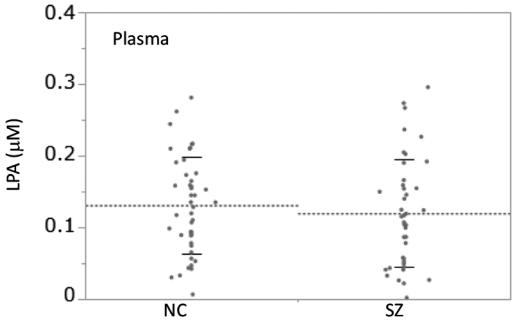

Fig. 2. Lysophosphatidic acid (LPA) levels in plasma samples. LPA levels (μM) were measured by enzyme-linked immunosorbent assay in 42 patients with schizophrenia (SZ) and 44 normal healthy controls (NC). Data are expressed as mean ± standard deviation. No significant differences between two groups was observed (Student's *t*-test. $P = 0.465$).

Table 2
Correlation between CSF LPA levels and PANSS scores in patients with schizophrenia.

PANSS score		All patients	Female patients	Male patients	Medicated patients	Unmedicated patients
Positive	*F*	$F(1,46) = 0.057$	$F(1,23) = 1.502$	$F(1,21) = 0.464$	$F(1,37) = 0.158$	$F(1,7) = 1.216$
	r_s	0.051	0.256	−0.106	0.063	−0.319
	P	0.812	0.233	0.503	0.694	0.307
Negative	*F*	$F(1,46) = 0.0069$	$F(1,23) = 0.238$	$F(1,21) = 0.072$	$F(1,37) = 0.122$	$F(1,7) = 0.335$
	r_s	−0.031	0.071	−0.116	−0.068	0.153
	P	0.934	0.631	0.792	0.729	0.581
General	*F*	$F(1,46) = 1.655$	$F(1,23) = 0.413$	$F(1,21) = 1.544$	$F(1,37) = 0.018$	$F(1,7) = 0.168$
	r_s	0.172	0.129	0.307	0.002	0.119
	P	0.205	0.527	0.228	0.895	0.694
Total	*F*	$F(1,46) = 0.561$	$F(1,23) = 0.910$	$F(1,21) = 0.097$	$F(1,37) = 0.007$	$F(1,7) = 0.003$
	r_s	0.067	0.151	0.051	−0.023	0.067
	P	0.458	0.350	0.759	0.936	0.957

The relationships between lysophosphatidic acid (LPA) levels in CSF and Positive and Negative Syndrome Scale (PANSS) scores in patients with schizophrenia were assessed by Spearman's rank correlation coefficient (r_s).

that LPA levels in CSF of schizophrenia patients were not significantly different from those of controls. On the other hand, LPA levels in CSF were significantly lower in medicated patients than unmedicated patients ($P = 0.038$), suggesting that our findings could be masked by the influence of the medications. These preliminary findings may also suggest that medication with antipsychotics could lower the CSF LPA levels in the patients. However, the number of medication-free patients was small. Therefore, we need to confirm our findings with a larger sample.

LPA is synthesized by autotaxin, which is a rate-limiting enzyme hydrolyzing lysophosphatidyl choline to LPA. Lysophosphatidyl choline is abundant in the blood and transported across the blood–brain barrier (Nguyen et al., 2014). Interestingly, it is reported that autotaxin is expressed in astrocytic perisynaptic lamellae engulfing excitatory synapses (Thalman et al., 2018). Lower LPA concentrations in medicated patients may results from lower activity of autotaxin in the brain. Moreover, LPA is rapidly degraded by lipid phosphate phosphatases, which are present in the synaptic compartment (Distler et al., 2014). Therefore, it is also possible that lower levels may results from higher activity of lipid phosphate phosphatases in the brain.

In the present study, we sought to determine whether plasma LPA levels could serve as a diagnostic indicator for schizophrenia. Diagnosis of schizophrenia largely depends on clinical interview and no established biochemical markers are available for everyday use in the clinical setting. Although the 'omics' approach is promising, lipid mediators such as LPA are not the focus in transcriptomic or proteomic approaches. On the other hand, so called lipidomic analysis were performed using plasma samples to evaluate biomarkers in schizophrenia patients (Aquino et al., 2018). However, levels of specific lipid mediators such as LPA were not reported. Therefore, the present study is the first to quantify plasma LPA levels in schizophrenia patients. In the present study, we found unaltered plasma LPA levels in schizophrenia patients compared with healthy controls. Our result suggests that LPA levels in plasma samples would not serve as a biomarker in the diagnosis of schizophrenia.

Finally, we examined correlation between PANSS score and LPA levels. In this study, no correlations were observed in CSF samples. On the other hand, we detected significant correlation between PANSS scores and plasma LPA levels, especially in males and unmedicated patients. This suggests that LPA levels in plasma samples may serve as a practical biomarker for use in subtyping or symptomatic assessment of schizophrenia.

There are several limitations to our study. Because of the exploratory nature of this research, we did not calculate the sample size in advance. The number of participants in each group was small. In particular, the number of medication-free patients with schizophrenia was small. Therefore, we need to replicate our study with a larger sample to confirm repeatability and validity of our findings. Additionally, this is a cross-sectional study. We will perform prospective sampling in future studies to examine the relationship between the LPA levels and antipsychotic medication in patients. It is reported that there is no specific circadian rhythm of plasma LPA levels in healthy subjects (Michalczyk et al., 2017). Further studies are needed to clarify the circadian rhythm of LPA levels in CSF. In addition, the storage time of CSF and plasma samples could also affect the LPA levels.

In conclusion, we demonstrated here that LPA levels in CSF of schizophrenia patients were not elevated when compare to those of normal healthy controls. Our result suggests that LPA levels in CSF and plasma samples would not serve as a diagnostic biomarker, but plasma levels could be used for symptomatic assessment of schizophrenia.

Table 3
Correlation between plasma LPA levels and PANSS scores in patients with schizophrenia.

PANSS score		All patients	Female patients	Male patients	Medicated patients	Unmedicated patients
Positive	*F*	$F(1,39) = 4.816$	$F(1,17) = 1.183$	$F(1,20) = 4.939$	$F(1,35) = 2.740$	$F(1,2) = 119.480$
	r_s	−0.321	−0.221	−0.477	−0.264	−1.000
	P	0.034	0.292	0.038	0.107	0.008
Negative	*F*	$F(1,39) = 0.2857$	$F(1,17) = 0.713$	$F(1,20) = 0.292$	$F(1,35) = 0.004$	$F(1,2) = 19.869$
	r_s	0.200	−0.074	0.113	−0.057	−0.949
	P	0.596	0.410	0.595	0.949	0.047
General	*F*	$F(1,39) = 5.895$	$F(1,17) = 1.138$	$F(1,20) = 5.815$	$F(1,35) = 3.448$	$F(1,2) = 555.067$
	r_s	−0.313	0.005	−0.472	−0.244	−1.000
	P	0.02	0.301	0.026	0.072	0.002
Total	*F*	$F(1,39) = 4.864$	$F(1,17) = 1.259$	$F(1,20) = 4.349$	$F(1,35) = 2.602$	$F(1,2) = 158.209$
	r_s	−0.352	−0.068	−0.460	−0.295	−1.000
	P	0.033	0.277	0.050	0.116	0.006

The relationships between lysophosphatidic acid (LPA) levels in plasma samples and Negative Syndrome Scale (PANSS) scores in patients with schizophrenia were assessed by Spearman's rank correlation coefficient (r_s).

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.01.052.

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