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REGULAR ARTICLE

Altered ethanolamine plasmalogen and phosphatidylethanolamine levels in blood plasma of patients with bipolar disorder

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Aim: Ethanolamine-containing phospholipids are synthesized in endoplasmic reticulum (ER) and mitochondria. ER stress and mitochondrial dysfunction have been implicated in bipolar disorder (BP). In this study, we aimed to examine the relationship of ethanolamine plasmalogen (PLE) and phosphatidylethanolamine (PTE) levels in blood plasma with BP.

Methods: Plasma PLE and PTE levels were compared between 34 patients with BP (DSM-IV) and 38 healthy control participants matched for age, sex, and ethnicity (Japanese). Furthermore, the relationships of plasma PLE and PTE levels with clinical variables were explored.

Results: Plasma PLE levels were significantly lower in patients with BP than in healthy controls (P = 0.0033). In subgroup analyses, plasma PLE levels were significantly lower in patients with BP type I (BP I) than in healthy controls (P = 0.0047); furthermore, plasma PTE levels were significantly lower in patients with BP I than in controls (P = 0.016) and patients with BP type II (BP II) (P = 0.010). Receiver-operating characteristic curve analysis revealed that the discriminatory power of plasma PTE levels for distinguishing between BP I and II was fair (area under the curve = 0.78; P = 0.0095). There were no significant correlations of plasma PLE or PTE levels with depression or manic symptoms in patients.

Conclusions: Plasma PLE and PTE levels were associated with BP I, but not with BP II. Moreover, plasma PTE levels differed between patients with BP I and II. Our findings highlight the importance of ethanolamine phospholipids in the pathophysiology of BP, especially BP I.

Keywords: *bipolar disorder, endoplasmic reticulum stress, ethanolamine plasmalogen, mitochondrial dysfunction, phosphatidylethanolamine.*

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Bipolar disorder (BP) is a severe psychiatric disorder characterized by recurrent episodes of mania and depression.[1] The aggregate lifetime prevalence rates are estimated at 1.0% for BP, 1.4% for subthreshold BP, and 2.4% for bipolar spectrum disorder worldwide.[2] BP has a lifelong impact on patients' overall health status, quality of life, and functioning.[3] BP is mainly categorized into two clinical subtypes: BP type I (BP I) and BP type II (BP II).[1] BP I is characterized by episodes of depression and the presence of mania, whereas BP II is characterized by episodes of depression and hypomania. Therefore, the main distinction between the two types is the severity of manic symptoms.[1] However, the pathophysiology of BP and pathophysiologic differences between these subtypes remain elusive.

Our group is the first to report reduced ethanolamine levels in the cerebrospinal fluid of patients with major depressive disorder,[4] indicating that ethanolamine and related molecules may play crucial roles in the pathophysiology of affective disorders. Ethanolamine plasmalogens (PLEs, also called plasmenylethanolamines) and phosphatidylethanolamines (PTEs) both have an ethanolamine head group.[5] There are two major biosynthetic pathways for PTE: the Kennedy pathway in endoplasmic reticulum (ER) and the phosphatidylserine decarboxylase reaction in mitochondria.[6] The Kennedy pathway is also crucial for the final steps of PLE production.[7] Plasmalogens constitute 15%–20% of total phospholipids in cell membranes and ≥ 50% of the glycerophosphoethanolamine fraction in the brain and other tissues. Furthermore, plasmalogens are significant components of subcellular membranes including those of the nucleus, ER, and mitochondria.[8] PTE is the second most abundant phospholipid in mammalian cells after phosphatidylcholine[9] and is especially plentiful in the inner mitochondrial membrane.[6]

ER stress and mitochondrial dysfunction have been implicated in BP.[10–12] Lithium and valproate are mood stabilizers widely used in the treatment of BP. Reportedly, lithium regulates the gene network for ER adaptation in lymphoblastoid cells derived from patients with BP[13] and valproate protects cells from ER stress-induced lipid accumulation and resultant apoptosis.[14] Long-term treatment with lithium or valproate enhances mitochondrial function *in vitro* and protects methamphetamine-induced neurotoxicity at the mitochondrial level *in vivo*.[15]

Recently, some postmortem brain studies have reported alterations in the levels of several plasmalogen species in patients with

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schizophrenia[16,17] and BP[17]; however, contradictive negative results have also been reported.[18–20] One study examined plasmalogen levels in red cell membrane among patients with BP I and healthy controls; however, there were no significant differences between the two groups.[21] To date, numerous studies have attempted to identify biomarkers for BP[22–27]; however, to our knowledge, none of these have explored the relationship of the blood plasma or serum ethanolamine phospholipid levels with BP.

We hypothesized that circulating PTE and/or PLE levels are altered in patients with BP compared with those in healthy controls. This study aimed to clarify the relationship of circulating PTE and/or PLE levels with the pathophysiology of BP. Moreover, a number of previous studies examining neurochemical differences between BP I and II,[28–30] hinted at the possibility that molecularly-based qualitative differences might underlie phenotypic differences between BP types I and II. This assumption prompted us to conduct subgroup analyses of BP I- and BP II patients.

Methods

Participants

Study participants comprised 11 patients with BP I, 23 patients with BP II, and 38 healthy controls matched for age, sex, and ethnicity (Japanese) (Table 1). They were recruited through the National Center of Neurology and Psychiatry (NCNP) hospital (Tokyo, Japan), advertisements in free local magazines, and our website. All participants were Japanese and belonged to the same geographical area (western metropolitan Tokyo) but were biologically unrelated. Trained psychologists/psychiatrists screened all participants using the structured Mini-International Neuropsychiatric Interview (M.I.N.I.),[31] Japanese edition.[32] A consensus diagnosis was made by at least two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition criteria,[33] and information from medical records, if available. Individuals with a medical history of central nervous system disease, severe head injury, or substance abuse/dependence were excluded. Individuals with a history of past or current contact with psychiatric services or a history of psychotropic drug use were excluded from the healthy control group.

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee at NCNP (A2014-141). All participants provided written informed consent.

Clinical assessments

Patients' symptoms were assessed using the Japanese version of the 21-item Hamilton Rating Scale for Depression (HAMD)[34,35] and the Japanese version of the Young Mania Rating Scale (YMRS).[36,37] Furthermore, physical parameters such as body height and weight were measured. Daily doses of antidepressants, antipsychotics, and benzodiazepine derivatives (anxiolytics and hypnotics) were converted to equivalent doses of imipramine, chlorpromazine, and diazepam, respectively, using a published guideline.[38] The converted values as well as daily lithium carbonate and sodium valproate doses were used in analyses.

Blood collection and analytical procedure

Blood collection was performed in a real-world setting without fasting, between 7:00 am and 3:45 pm. Venous blood was drawn into ethylenediamine tetra-acetic acid disodium (EDTA-2Na) vacutainer tubes (Terumo, Tokyo, Japan). The blood was immediately placed on ice and then centrifuged at 2500 × *g* at 4°C for 15 min; aliquots of the supernatant were distributed into microtubes and stored at −80°C.

Samples from all participants were sent to Phenomenome Discoveries, Inc. (PDI; Saskatoon, Saskatchewan, Canada) from NCNP in a frozen state and stored under −80°C until analysis. Ethanolamine phospholipid levels were measured at PDI in a blinded manner (i.e. blind to participant information). The samples were randomized before analysis and assayed using PDI's glycerophosphoethanolamine (PTEs, PLEs) panel.

Determination of plasma PLE and PTE levels

In the PDI laboratory, analytes were extracted from plasma into ethylacetate using a pH-adjusted liquid/liquid extraction procedure. Analyte intensities were measured through a direct injection of the extraction solution into an Ionics 3Q tandem mass spectrometer operating in the negative ionization atmospheric pressure chemical ionization mode. For PLE analytes, the (M-H)- ion was selected by Q1 to be fragmented in the collision cell and the sn-2 (R-COO-) ion was selected by Q3 and used as the daughter ion for detection.

Table 1. Demographic and clinical information of the study participants

	HC	BP type I	BP type II	Statistics †
n (F/M)	38 (23/15)	11 (7/4)	23 (12/11)	$\chi^2 = 0.56$, $df = 2$, $P = 0.76$
Age, year	45.9 ± 11.3	47.0 ± 13.6	44.5 ± 12.8	$F = 0.18$, $df = 2$, $P = 0.83$
BMI, score	22.8 ± 3.3	24.5 ± 5.6	23.0 ± 4.4	$F = 0.75$, $df = 2$, $P = 0.47$
HAMD-21, score	—	12.9 ± 8.5	19.1 ± 8.9	$t = -1.93$, $df = 32$, $P = 0.063$
YMRS, score	—	15.6 ± 8.9 ‡	4.7 ± 6.6 ‡	**$t = 3.89$, $df = 30$, $P = 0.00051$**
AD, mg	—	39.8 ± 89.9 ‡, §	130.5 ± 130.8 ‡, §	**$t = -2.36$, $df = 27.63$, $P = 0.026$**
AP, mg	—	209.4 ± 311.1 ‡, §	179.2 ± 343.1 ‡, §	$t = 0.24$, $df = 31$, $P = 0.81$
BZD, mg	—	12.5 ± 12.0 ‡, §	21.3 ± 17.7 ‡, §	$t = -1.43$, $df = 30$, $P = 0.17$
Lithium carbonate, mg	—	272.7 ± 412.5 ‡, §	139.1 ± 369.0 ‡, §	$t = 0.95$, $df = 32$, $P = 0.35$
Sodium valproate, mg	—	181.8 ± 260.1. ‡, §	52.2 ± 147.3 ‡, §	$t = 1.54$, $df = 13.16$, $P = 0.15$
8:00 a.m.–blood sampling, min	334.2 ± 105.3	327.1 ± 141.9	292.7 ± 100.3	$F = 1.05$, $df = 2$, $P = 0.36$

Continuous values are expressed as mean ± standard deviation.
†Statistical values were derived from chi-squared test, analysis of variance, and *t*-test. Significant results are in bold type.
‡Ambiguous data were excluded.
§When a drug class was not prescribed, the dose was considered to be zero.
AD, imipramine equivalent daily dose of antidepressants; AP, chlorpromazine equivalent daily dose of antipsychotics; BMI, body mass index; BP, patients with bipolar disorder; BZD, diazepam equivalent daily dose of benzodiazepine derivatives; HAMD-21, Hamilton Depression Rating Scale 21-item version; HC, healthy controls; YMRS, Young Mania Rating Scale.

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For PTE analytes, the (M-H)- ion was selected by Q1 to be fragmented in the collision cell and the sn-1 (R-COO-) ion was selected by Q3 and used as the daughter ion. The exception was PTE 18:0/20:5, where the sn-2 (R-COO-) ion was used for detection. Analyte values were determined using a standard stable isotope dilution protocol, wherein a constant amount of a non-endogenous stable isotope (^{13}C6-PLE 16:0/22:6 and ^{13}C19-PTE 16:0/22:6) was added to all unknown plasma samples. The peak height ratio of each PLE and PTE species to the respective stable isotope was then determined. Finally, the relative intensities of PTE and PLE subspecies were summed as total values to be used for further analyses.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD). Demographic and clinical data were compared using analysis of variance and *t*-test, and distributions of categorical data were tested using the χ^2 test. Because the general linear model presumes normal distribution of data, we used logarithmic transformation of data for analysis of covariance (ANCOVA). ANCOVA was used to compare log-transformed relative intensities of plasma PLE and PTE levels between diagnostic groups, controlling for age, sex, and body mass index (BMI). When *post hoc* pairwise tests comparing the three groups (controls and BP I and II groups) were performed, Bonferroni correction was applied. We used non-parametric receiver operating characteristic (ROC) curves to estimate the power of PLE/PTE values to discriminate between the examined cohorts of BP I and BP II patients, while, controlling for age, sex, and BMI by using residual plots. The relationships of plasma PLE and PTE levels with symptoms and daily doses of psychotropic drugs in BP patients were assessed using a non-parametric partial correlation test controlling for age, sex, and BMI. Differences with a two-tailed *P*-value <0.05 were deemed statistically significant. Analyses were performed using IBM SPSS Statistics 22.0 (IBM Japan, Tokyo, Japan).

Results

Demographic and clinical data of the participants are shown in Table 1. There were no significant differences in sex distributions, mean age, or BMI across the three diagnostic groups. In patients, YMRS scores were significantly higher in the BP I group compared with the BP II group ($P = 0.00051$). BP II group showed significantly higher daily dose of antidepressant than BP I group ($P = 0.026$).

Comparisons of plasma PLE levels

ANCOVA analysis with age, sex, and BMI as the covariates showed a significant main effect of diagnosis on the log-transformed plasma PLE levels ($F = 9.29$, $df = 1$; $P = 0.0033$) between the BP and control groups. Patients with BP showed significantly lower plasma PLE levels than controls (Fig. 1a). To exclude the possibility that comorbid physical illnesses or related drug treatment confounded the results, we performed additional analyses only in subjects without physical comorbidities or associated medication. Even in these subjects, plasma PLE levels were significantly lower than those in healthy controls ($F = 4.83$, $df = 1$; $P = 0.032$; Fig. S1a). In regard to subgroup analyses, Figure 1c shows the results of *post hoc* pairwise comparisons between the diagnostic groups. Plasma PLE levels were significantly lower in patients with BP I compared with healthy controls ($P = 0.0047$). There were no significant differences in plasma PLE levels between BP I and BP II ($P = 0.32$) or BP II and controls ($P = 0.13$).

Comparisons of plasma PTE levels

In ANCOVA analysis with age, sex, and BMI as covariates, no significant main effect of diagnosis (BP *vs*. control) on the log-transformed plasma PTE levels ($F = 0.81$, $df = 1$; $P = 0.37$) was found (Fig. 1b). In an additional analysis restricted to subjects without comorbid physical disease or related medication, no significant difference was found between patients with BP and controls (Fig. S1b). As regards subgroup analyses, Figure 1d shows the results of *post hoc* pairwise comparisons between diagnostic groups. The plasma PTE level was significantly lower in patients with BP I compared with healthy controls (corrected $P = 0.016$) or BP II (corrected $P = 0.010$); there was no significant difference between BP II and controls (corrected $P = 1.0$).

Because the BP I and II groups had significantly different YMRS scores, we examined whether the difference in plasma PTE between BP type I and II could be attributed to manic symptoms. We conducted non-parametric partial correlation analysis controlling for age, sex, and BMI. The correlation coefficients of PTE with YMRS score were not significant in both BP I ($\rho = -0.43$, $df = 5$; $P = 0.33$) and BP II ($\rho = 0.019$, $df = 17$; $P = 0.94$) (Fig. S2). Thus, the observed decrease in plasma PTE was probably related to diagnostic characterization rather than a difference in manic symptoms *per se*.

We conducted a non-parametric ROC curve analysis to estimate the power of plasma PTE values to discriminate between BP I and II, adjusting for age, sex, and BMI. The calculated area under the curve (AUC) was 0.78 ($P = 0.0095$) (Fig. 2b), indicating that PTE had fair (0.70–0.80) discriminatory power. Meanwhile plasma PLE also showed fair discriminatory power (AUC = 0.72, $P = 0.041$; Fig. 2a).

Relationships of plasma PLE and PTE levels with symptoms and psychotropic medication

We conducted additional non-parametric partial correlation analyses controlling for age, sex, and BMI. In the patient groups (BP I + BP II), there were no significant correlations of plasma PLE or PTE levels with HAMD-21 (PLE: $\rho = 0.067$, $df = 29$; $P = 0.72$; PTE: $\rho = 0.070$, $df = 29$; $P = 0.71$) or YMRS total scores (PLE: $\rho = 0.054$, $df = 27$; $P = 0.78$; PTE: $\rho = -0.34$, $df = 27$; $P = 0.072$). Table 2 shows the relationships between plasma PLE and PTE levels and daily equivalent doses of each class of psychotropic drug. There were no significant correlations of plasma PLE levels with dosing in any of the examined drug classes. Daily doses of sodium valproate showed a

Table 2. Non-parametric partial correlation tests between PLE or PTE levels in blood plasma and daily psychotropic drug doses

	AD			AP			BZD			Lithium carbonate			Sodium valproate		
	ρ	*df*	*P*	ρ	*df*	*P*	ρ	*df*	*P*	ρ	*df*	*P*	ρ	*df*	*P*
PLE	0.29	29	0.11	0.0040	28	0.98	0.25	27	0.19	−0.31	29	0.091	−0.038	29	0.84
PTE	0.27	29	0.14	−0.19	28	0.31	0.23	27	0.23	−0.17	29	0.36	−0.44	29	0.014

Results derived from non-parametric partial correlation tests controlling for age, sex, and BMI.
When each class of drugs was not medicated, the dose was considered to be zero.
AD, imipramine equivalent daily dose of antidepressants; AP, chlorpromazine equivalent daily dose of antipsychotics; BZD, diazepam equivalent daily dose of benzodiazepine derivatives; PLE, ethanolamine plasmalogens; PTE, phosphatidylethanolamine.

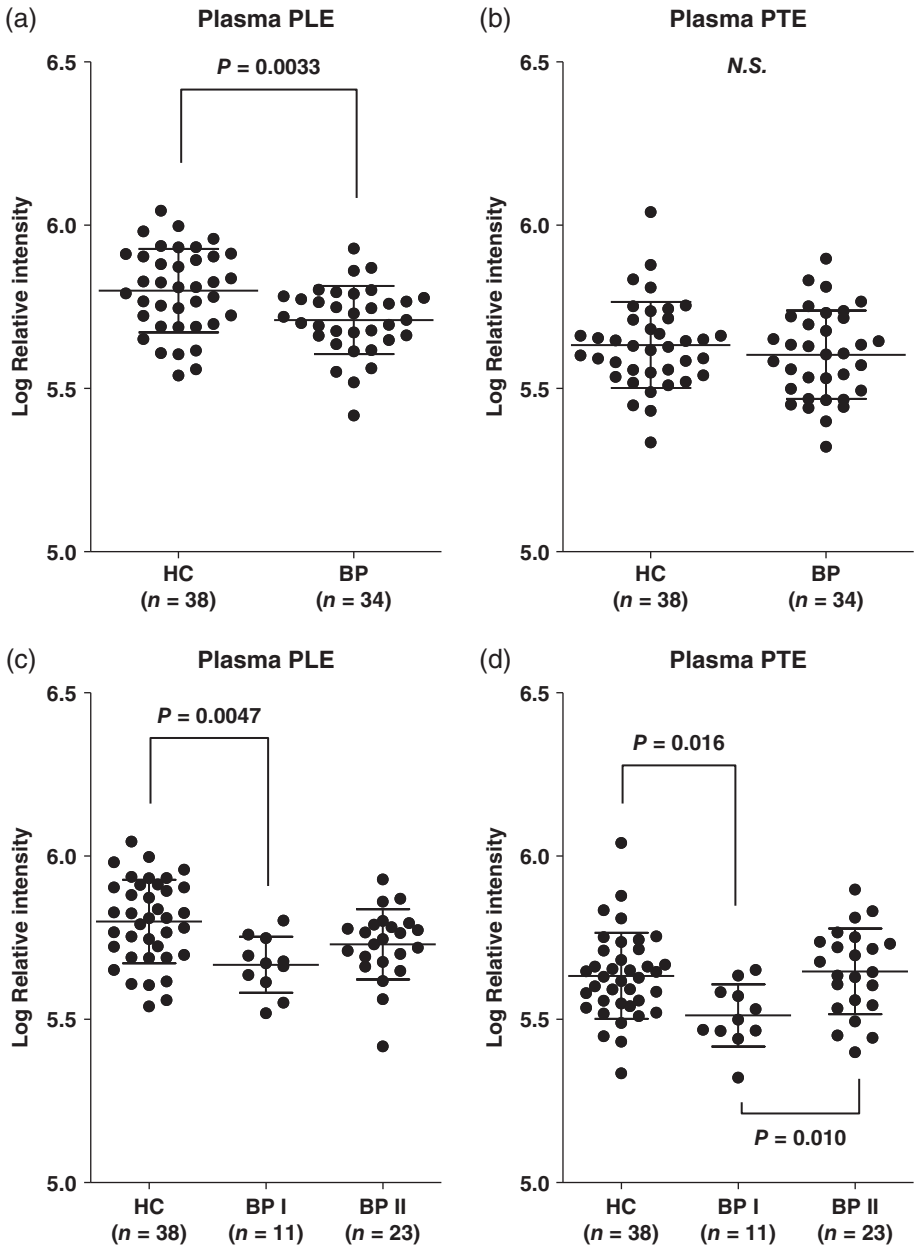

Fig.1 Dot plots of PLE and PTE levels (log transformed) in blood plasma of the BP patient and healthy control groups. Dot plots showing plasma levels of (a) PLE in healthy controls (HC) and patients with BP; (b) PTE in HC and BP patients; (c) PLE among HC and BP I and II; and (d) PTE among HC and BP I and II. Central horizontal bars represent mean values of the groups, and both upper and lower horizontal bars represent standard deviations. Data are expressed as log-transformed relative intensities as measured by a tandem mass spectrometer. Statistical analyses were conducted by analysis of covariance, controlling for age, sex, and body mass index. In the panel (c) and (d), *P*-values were derived from pairwise comparisons and adjusted by Bonferroni correction. Abbreviations: BP I/II, patients with bipolar disorder type I or II; PLE, ethanolamine plasmalogens; PTE, phosphatidylethanolamine.

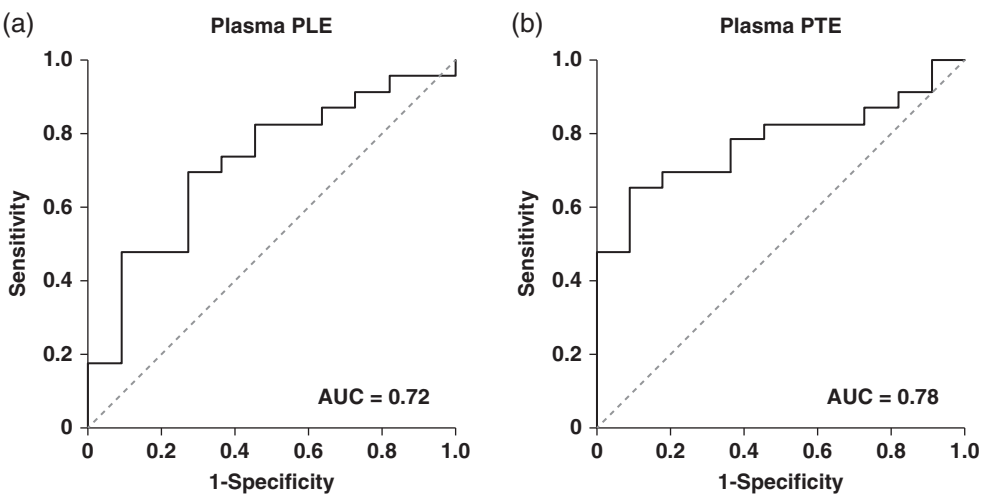

Fig.2 Non-parametric ROC curve analysis showing the ability of PLE and PTE to discriminate between patients with BP I and II. Receiver-operating characteristic (ROC) curve analysis adjusted for age, sex, and body mass index on the relative intensities of (a) ethanolamine plasmalogen (PLE); and (b) phosphatidylethanolamine (PTE) in blood plasma, depicting the sensitivity and specificity of discriminations between patients with bipolar disorder (BP) subtypes I and II. The area under the curve (AUC) of PLE and PTE were 0.72 (P = 0.041) and 0.78 (P = 0.0095), respectively, indicating fair discriminatory abilities.

weakly negative correlation with plasma PTE levels (ρ = −0.44, df = 29, P = 0.014; Table 2).

Discussion

This study aimed to examine whether PLE and/or PTE levels were associated with BP and its clinical variables. We found that plasma PLE levels were significantly lower in patients with BP compared to controls, and this result persisted even when the examined subjects were restricted to those without comorbid physical disease or related medication. In subgroup analyses, we found that plasma PLE levels in patients with BP I were significantly lower than those in healthy controls. We also found that plasma PTE levels were significantly lower in the patients with BP I compared with healthy controls and patients with BP II. There was no significant correlation of plasma PLE and PTE with the severity of depression or the severity of manic symptoms among BP I or II patients, nor any significant relationship between the administered doses of psychotropic medication and plasma PLE. On the other hand, plasma PTE levels were significantly correlated with the height of daily doses of sodium valproate in BP patients.

Contrary to our observations of significantly reduced plasma PLE levels in patients with BP compared to those in healthy controls, and significantly lower plasma PLE levels in patients with BP I than in controls, McNamara *et al*.[21] reported no such significant group differences. However, they analyzed plasmalogen levels localized in red blood cell membranes. Like many components of the serum and blood plasma, circulating plasmalogens are considered to originate mainly from the liver,[39] and circulating plasmalogen levels reflect peroxisomal and ER functions.[6,39] Plasmalogens are critical endogenous antioxidants and are known to be affected by factors such as inflammation.[40] Indeed, mice administered lipopolysaccharide showed significantly decreased PLE, but not PTE, levels in the prefrontal cortex and hippocampus.[41] Moreover, the activation of NOD-like receptor family pyrin domain-containing three (NLRP3) inflammasome was observed in patients with BP.[42]

In a subgroup analysis, we found significantly reduced plasma PTE levels in patients with BP I compared with BP II and healthy controls. Mitochondrial dysfunction and activation of the inflammatory system are two of the most consistently reported findings in BP, and a potential link between mitochondrial dysfunction and the NLRP3 inflammasome that triggers the inflammatory cascade in BP has also been suggested.[43] Mitochondrial dysfunction could partly explain the reduction in PTE levels observed in our patients with BP I. Since BP I is characterized by manic episodes, we examined the relationship between plasma PTE levels and manic symptoms. However, we found no significant correlation. Therefore, the manic symptoms may not be directly related to changes in plasma PTE levels. Accordingly, blood PTE levels may differ depending on the subtypes of BP, making it a potential marker of mitochondrial dysfunction.

Collectively, the low levels of ethanolamine phospholipids are more specifically related to BP I. We found no significant differences in either plasma PLE- or PTE levels between patients with BP II and healthy controls in subgroup analyses. Therefore, ethanolamine phospholipids levels are more associated to BP I than to BP II related pathological processes. Associations of BP and genetic variants of mitochondrial functions[44–47] and ER stress[48–50] have been reported, and the links between mitochondrial dysfunction, ER stress, and inflammatory status may be more relevant to the pathophysiology of BP subtype I. The interaction of genetic variation of B-cell CLL/lymphoma 2 (BCL-2) and its expression was shown in BP I patients specifically[51]; BCL-2 is located in both mitochondria and ER and has various roles including anti-apoptosis and intracellular calcium homeostasis. Furthermore, among several blood cytokines reportedly increased in patients with BP, specific molecules such as soluble tumor necrosis factor alpha receptor type 1 were significantly more elevated in BP type I compared with type II.[52]

Because plasma PLE and PTE levels did not correlate with symptom severity in our patients, they might be trait markers rather than state markers of BP. Furthermore, the difference in plasma PTE levels between patients with BP I and II indicated that plasma PTE levels could be used as a subtyping marker of BP. Indeed, the ROC curve analysis showed a fair discriminatory power for plasma PTE, though plasma PLE also showed a fair discriminatory power on BP I and II.

There were several limitations in this study. First, since the number of patients with BP I was small (n = 11), there might be type II errors in the PLE results attributable to low statistical power. To rule out this possibility, a study with a larger sample size will be necessary. Second, the measurement of plasma ethanolamine phospholipid levels was conducted in a real-world setting. Most of the patients were medicated, and blood sampling was not performed after overnight fasting or at a fixed time. However, we did not observe any significant correlation of PLE or PTE with psychotropic medication other than valproate, or blood sampling time (PLE: ρ = −0.057, df = 70; P = 0.63; PTE: ρ = −0.030, df = 70; P = 0.81). Third, it could also be that the observed differences between BP I and BP II patients may have arisen from the different number of manic/depressive episodes. Unfortunately, we did not have accurate information about the number of episodes for each patient. To resolve this issue, future studies should obtain detailed information on the number of episodes to clarify its possible effect on plasma PTE levels. Fourth, plasma PTE levels showed a negatively weak correlation with daily dose of sodium valproate. However, since plasma PTE levels correlated with YMRS scores in patients at a tendency level (P = 0.072), it is possible that the observed correlation could have been confounded by the severity of manic symptoms. Indeed, when a non-parametric, partial correlation analysis was performed after including YMRS score as a covariate, the correlation was not significant (ρ = −0.32, df = 26; P = 0.099), indicating that the observed reduction in plasma PTE levels cannot be attributed solely to valproate medication. To clarify the effect of valproate on plasma PTE levels, future studies will be needed.

In conclusion, plasma PLE levels in patients with BP were significantly lower than those in healthy controls. In subgroup analyses, the plasma PLE level in BP I patients was significantly lower than that of healthy controls, while the plasma PTE level in BP I patients was significantly lower than that of controls and patients with BP II. The PLE and PTE levels did not correlate with symptom severity. Compared with healthy controls, plasma PLE and PTE levels were associated with BP I, but not with BP II. Moreover, plasma PTE differed between the subtypes of BP I and II. Our findings point to the importance of ethanolamine phospholipids in the pathophysiology of BP, especially BP I.

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Disclosure statement

D. Goodenowe and Y. Yamazaki were a former CEO and a former employee of Phenomenome Discoveries, Inc. (Saskatoon, Saskatchewan, Canada), respectively. The other authors declare no conflict of interest.

Author contributions

S.O. conducted the data analyses and wrote the draft of the manuscript. D.G. measured and analyzed the plasmalogen ethanolamine and phosphatidylethanolamine levels in blood plasma of study subjects. Y.Y. managed sample measurement procedures and the study protocol. K.H., S.Y., M.O., S.H., R.M., Y.Y., I.I, and J.M. carried out psychiatric assessments and obtained demographic and clinical information from the study subjects. K.H., S.Y., M.O., and S.H. collected the blood samples. K.H., S.Y., Y.Y., I.I., and J.M. recruited participants. T.M. managed study subject's information and plasma samples. H.K. designed the study, supervised the data analysis, and the writing of the paper. All authors contributed to and have approved the final manuscript.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Dot plots of (log transformed) ethanolamine plasmalogen and phosphatidylethanolamine levels in blood plasma of bipolar disorder patients and healthy controls without physical comorbidities or related medication.

Figure S2. Scatter plot showing the relationship between plasma phosphatidylethanolamine level and Young Mania Rating Scale score.