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^{31}P Nuclear magnetic resonance spectroscopy findings in bipolar illness: a meta-analysis

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Abstract

Published literature comparing ^{31}P MR brain spectra of bipolar patients to healthy controls was evaluated, focusing on phosphomonoester (PME)/phosphodiester (PDE) resonance areas because these metabolites are related to membrane phospholipids and membrane defects in bipolar disorder have been suggested. Studies comparing PME and/or PDE values of bipolar subjects to values observed in healthy controls were reviewed. Data from the studies meeting our inclusion criteria (8 reports involving 139 bipolar and 189 comparison subjects) were grouped according to the mood state of the subjects. Meta-analyses of data were performed to compare PME and PDE levels of euthymic bipolar patients to healthy controls, as well as comparing PME levels during euthymia in bipolar subjects to values observed during manic and depressed states. The PME values of euthymic bipolar patients were found to be significantly lower than PME values of healthy controls. Depressed bipolar patients had significantly higher PME values in comparison to euthymic bipolar patients. No significant difference could be detected between the PDE values of bipolars and controls. This meta-analysis found support for trait- and possibly state-dependent abnormalities of membrane phospholipid metabolism, which may reflect a dysregulation in brain-signal transduction systems of relevance in bipolar illness.

Keywords: Phosphomonoesters; Phosphodiesters; Brain phosphorous metabolism

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1. Introduction

Bipolar illness has devastating effects on the lives of millions owing to its prevalence, chronicity and severity (Goodwin and Jamison, 1990; Simpson and Jamison, 1999). In spite of ongoing research, the etiopathogenesis of bipolar illness has not been elucidated (Manji et al., 1999).

Considering the highly specialized organization of the human brain, controversial aspects of postmortem and in vitro studies and the lack of experimental or animal models of bipolar illness, in vivo studies of human brain hold considerable potential for providing essential information regarding the pathophysiology of bipolar illness. Among the techniques available for in vivo investigation of human brain, magnetic resonance spectroscopy (MRS) is of special relevance as it can be used to obtain neurochemical information, which is unavailable with the other in vivo techniques (Soares et al., 1996; Kato et al., 1998). Thus, data provided by MRS, when combined with the data from molecular neuropsychiatry research and also with the results from structural and functional neuroimaging studies, may enable us to develop an integrated structural–functional model of bipolar illness and elucidate some of the mechanisms which underlie the disease process.

MRS studies of several different nuclei, such as ^{1}H, ^{31}P, and ^{7}Li, have relevance to bipolar illness (Soares et al., 1996; Kato et al., 1998). Among these, ^{31}P MRS has been used most extensively, and considerable data have been accumulated. In an attempt to combine data and overcome power limitations associated with small sample sizes, we performed meta-analyses of the ^{31}P MRS studies of bipolar illness on cerebral metabolites, phosphomonoesters (PMEs, consisting of phosphocholine, phosphoethanolamine, phosphoserine and sugar phosphates such as inositol-1-monophosphate) and phosphodiesters (PDEs, consisting of glycerophosphocholine, glycerophosphoethanolamine and mobile phospholipids), since these metabolites are related to membrane phospholipids and membrane phospholipid abnormalities have been suggested in bipolar disorder (Meltzer 1991; Kato et al., 1998). As membrane phospholipid metabolism is critically involved in the signal transduction processes and gene expression, any defect in this system may involve key regions of the brain circuits which participate in mood regulation.

We addressed the following questions:

1. Is there a difference in the PME peak area of bipolar patients in the euthymic state in comparison to healthy controls?
2. Is there a difference in the PME peak area of bipolar patients in the depressed state in comparison to healthy controls and bipolar patients in the euthymic state?
3. Is there a difference in the PME peak area of bipolar patients in the manic state in comparison to healthy controls and bipolar patients in the euthymic state?
4. Is there a difference in the PDE peak area of bipolar patients in the euthymic state compared to healthy controls?
5. Are there differences in the PDE peak areas of bipolar patients in the depressed and/or manic state in comparison to healthy controls and bipolar patients in the euthymic state?

2. Method

2.1. Selection of studies

A computer-assisted literature search of the National Library Medicine's Medline and Health Gate Medline files through 1978 has been made by using '^{31}P magnetic resonance spectroscopy' and 'bipolar illness' as key words. Augmented by the use of citations from the review articles on this topic, this process yielded eight publications. The ^{31}P MRS studies of in vivo human brain were included in the data analysis only if:

1. Bipolar patients in either the euthymic, manic, or depressed state were compared to healthy comparison subjects.
2. Mole percent PME and/or PDE values and standard deviations (S.D.) were provided.

2.2. Meta-analysis procedure

Two principal types of linear statistical models are used to analyze groups of studies: fixed effects models and random effects models. Both approaches yield a pooled effect size, which is a weighted average of the effect size for each study. Fixed-effects models assume that the variation in effect size is largely due to the size of the study. Random-effects models include a second source of variation, which is between-study variations in the effect size. A notable difference between the two approaches is that random effects models give wider confidence intervals for the pooled effect size when there is heterogeneity between studies used in the analysis. Both fixed effects and random effect models were fit to the data. However, as discussed below, we elected to report the random effects results in all cases to be conservative.

Since our set of studies provided means and S.D.s of the comparison groups, we elected to use 'Hedge's *g*' to conduct the meta-analysis. 'Hedge's '*g*' is a dimensionless effect size, defined as the difference between the means of the two compared groups divided by the pooled standard deviation (Cooper and Hedges, 1994). Homogeneity of the effect size was tested with the *Q*-statistic (Cooper and Hedges, 1994). In the case of PME euthymic vs control and PME manic vs euthymic the *Q*-statistic indicated that the studies were heterogeneous. Heterogeneity between studies can be compensated for by a covariance analysis and random effects models. In our case, with the relatively few studies in each group, we elected to forgo a covariance analysis and rely on the results of the random effects model. This model includes an estimate of the variance between studies as well as variance due to study size. Confidence intervals were calculated using normal approximations. No correction was made for multiple uses of studies in the comparisons.

First we applied this meta-analysis procedure to six studies, which provided sufficient data for the comparison of the PME levels in euthymic bipolar patients to healthy controls. Then, we performed separate meta-analyses, comparing PME levels of depressed and manic bipolar patients to healthy controls and also to euthymic bipolar patients. Finally, we meta-analyzed the PDE levels of euthymic bipolar patients in comparison to healthy controls. Whenever the authors provided measurement averages for the right and the left hemisphere separately, we elected to use the measurements for the right hemisphere, since there is some data suggesting right hemisphere involvement in mania (Cummings and Mendez, 1984; Starkstein et al., 1987, 1991).

As there was an overlap of subjects between some studies, the study with the largest possible *N* (sample size) was selected for inclusion, whenever studies with common patients were to be excluded from the analysis. Analyzing the studies in this way will reduce bias in the estimate of the pooled effect size and provide a conservative (larger) estimate of the between-study variance in the random effects models. In all but one case, PDE euthymic vs. control, the pooled effect size was reduced by dropping a study from the meta-analysis.

To perform the meta-analyses, we used a computer program written in house (DJD). The program was written in *R* (Pinheiro and Bates, 2000), an implementation of the *S* language (Becker et al., 1988). The program follows the *SAS* code provided in Cooper and Hedges (1994), in which the authors actually provide three slightly different estimates of the between-study variance component in the random effects model. The estimate yielding the least significant result, the unweighted variance estimate, is reported.

3. Results

The inclusion process identified eight reports (Kato et al., 1991, 1992, 1993, 1994a,b, 1995; Deicken et al., 1995a,b). All eight studies reported mol.% PME values of euthymic bipolar patients relative to healthy controls, while three of them included mol.% PME values of bipolar patients in the manic state (Kato et al., 1991, 1993, 1995) and three in the depressed state (Kato et al., 1992, 1994b, 1995). However, as there was a significant overlap in some of these study samples, we excluded two sets of data (Kato et al.,

1993, 1994b) from the analysis comparing PME values of euthymic bipolar patients to those of healthy controls and performed meta-analysis in the six remaining studies. Although PME resonance areas were computed from different brain regions, to be conservative, we performed another meta-analysis by dropping data from Deicken et al. (1995a), as there was an overlap of subjects between the studies by this group. For the analyses of state-dependent alterations, first we meta-analyzed three studies for each; then to avoid any erroneous conclusions, we excluded one study from the comparison of PME depressed and PME euthymic (Kato et al., 1992), and one from the comparison of PME manic and PME euthymic (Kato et al., 1991). We performed meta-analyses in the two studies left for each and report these findings as well as the original ones, since these overlaps were only partial.

Among the eight studies, only four provided data for the mol.% PDE values of euthymic bipolar patients in comparison to healthy controls (Kato et al., 1992, 1993; Deicken et al., 1995a,b), one for the mol.% PDE values of depressed in comparison to euthymic bipolar patients and healthy controls (Kato et al., 1992), one for the mol.% PDE values of manic in comparison to euthymic bipolar patients and healthy controls (Kato et al., 1993). Thus, analyses of PDE peak area of bipolar patients in the depressed and/or manic state in comparison to healthy controls and bipolar patients in euthymic state could not be performed.

The diagnostic status and spectral acquisition parameters for each study are documented in Table 1, as well as the weights and the effect sizes. Among the eight studies, bipolar subtypes were not specified in three studies (Kato et al., 1992; Deicken et al., 1995a,b), only bipolar-I and NOS were included in one (Kato et al., 1994a), all bipolar subtypes were included in two (Kato et al., 1993, 1995) studies, while for the other two only data from the patients with bipolar-I diagnoses were included (Kato et al., 1991, 1994b). Two studies withheld all psychotropic medications for 1 week prior to the ^{31}P MRS acquisition date (Deicken et al., 1995a,b), while the others obtained the ^{31}P MR spectra of patients who were mostly on psychotropic medications including lithium. Five of the eight studies used identical acquisition parameters (Kato et al., 1991, 1992, 1993, 1994a,b) (Table 1). In three studies, spectra were processed in a randomized and blind manner by a single operator to eliminate interoperator variance (Kato et al., 1995; Deicken et al., 1995a,b). For the other five studies, spectra were processed without blinding. However, inter-assay intra-individual coefficients of variation in bipolar subjects as well as inter-individual coefficients of variation in normal subjects were reported in all but one study, in which intrarater coefficients of variation for peak fitting and inter-assay intra-individual coefficients of variation in patients were reported.

All the eight studies have used controls whose ages and sexes were either comparable or matched to the patients, except for one study (Kato et al., 1994b).

The results for 11 comparisons performed appear in Table 2. The random effects z score is the pooled effect size (weighted average for the random effects model) divided by its standard deviation. The 95% confidence intervals for the pooled effect size and P-value corresponding to z are provided in Table 2. There was a significant pooled effect size for the comparison of PME levels in euthymics vs. controls. The sign of the effect indicates that bipolar euthymics had lower PME levels than controls (for the meta-analysis over the six studies, $P = 0.014$; for the meta-analysis over the five studies, $P = 0.046$; Tables 1 and 2). No significant alteration in PDE values of bipolar euthymics compared to controls was detected ($P = 0.597$, Tables 2 and 3). The second significant pooled effect size was observed for the comparison of PME levels in depressed vs. euthymic bipolar subjects. Bipolar patients with current depressive episodes had higher PME levels than bipolar euthymics (for the meta-analysis over the three studies, $P = 0.0005$; for the meta-analysis over the two studies, $P = 0.01$, Tables 2 and 4). No significant association, however, could be detected for PME levels in manic vs. euthymic subjects (for the meta-analysis over the three studies, $P = 0.247$; for the meta-analysis over the two studies, $P = 0.60$, Tables 2 and 5). There was no

Table 1
The effect sizes and spectral acquisition methods of the studies included in the meta-analysis on comparison of the PME levels of euthymic bipolar patients and healthy controls*

Study	*PME* Control	*N* Control	Age Mean ± S.D.	*PME* Bip. euthymic	*N* Bip. euthymic	Age Mean ± S.D.	*g*
Deicken et al., 1995a[a]	14.0 ± 3.6	14	39.8 ± 10.2	10.5 ± 3.7	12	40.1 ± 8.3	−0.96
Deicken et al., 1995b	13.0 ± 3.9	16	39.9 ± 11.1	11.2 ± 3.2	12	40.3 ± 8.7	−0.5
Kato et al., 1992	12.2 ± 1.4	10	40.8 ± 9.1	9.4 ± 1.7	10	41.9 ± 8.4	−1.8
Kato et al., 1994a	11.2 ± 1.5	60	39.6 ± 13.9	10.6 ± 1.7	40	42.0 ± 12.4	−0.38
Kato et al., 1991	11.0 ± 1.0	9	39.8 ± 10.9	9.0 ± 1.0	9	44.1 ± 9.1	−2.00
Kato et al., 1995	10.9 ± 3.4	21	42.5 ± 10.2	11.2 ± 2.5	17	40.4 ± 9.2	0.1
Kato et al., 1994b[b]	–	59	38.1 ± 12.6	–	12	44.0 ± 9.7	–
Kato et al., 1993[b]	–	17	39.1 ± 10.1	–	17	40.1 ± 10.8	–

Study	Weight	Acquisition method	*TR*	*TE*	*ROI*	Coil	Field strength
Deicken et al., 1995a[a]	1.98	Spin-echo sequence	350 ms	3.5 ms	Temporal lobe	Quadrature birdcage	2 *T*
Deicken et al., 1995b	2.07	Spin-echo sequence	350 ms	3.5 ms	Frontal lobe	Quadrature birdcage	2 *T*
Kato et al., 1992	1.63	DRESS	3 s	–	Frontal lobe	Surface coil for ^{31}P MRS	1.5 *T*
Kato et al., 1994a	2.67	DRESS	3 s	1.5 ms	Frontal lobe	Surface coil for ^{31}P MRS	1.5 *T*
Kato et al., 1991	1.50	DRESS	3 s	–	Frontal lobe	Surface coil for ^{31}P MRS	1.5 *T*
Kato et al., 1995	2.28	Phase-encoding	2 s	1 ms	Frontal lobe	Surface coil for ^{31}P MRS	1.5 *T*
Kato et al., 1994b[b]	–	DRESS	3 s	–	Frontal lobe	Surface coil for ^{31}P MRS	1.5 *T*
Kato et al., 1993[b]	–	DRESS	3 s	–	Frontal lobe	Surface coil for ^{31}P MRS	1.5 *T*

*PME: Phosphomonoesters; N = sample size; TR: repetition; TE: echo time; ROI: region of interest; g = effect size, weights are reported over the random effects.

[a]Although measurements of PMEs were from different brain regions, data were reanalyzed by dropping this study, as there was some degree of overlap in subjects.

[b]Meta-analysis was performed over the six studies, as there was an overlap of subjects.

significant difference between PME levels in depressed or manic states vs. control (for the meta-analysis over the three studies, $P = 0.488$; for the meta-analysis over the two studies, $P = 0.29$; for the meta-analysis over the three studies, $P = 0.288$; for the meta-analysis over the two studies, $P = 0.65$, respectively; Table 2).

4. Discussion

This meta-analysis found support for trait-dependent alterations of PME levels in bipolar illness. In regard to state-dependent alterations, the number of studies meta-analyzed for that issue is too small for definitive conclusions. However, the present findings suggest some state-dependent alterations in bipolar depression.

The PME resonance obtained with ^{31}P MRS has contributions from phosphocholine, phosphoethanolamine, phosphoserine and sugar phosphates including inositol-1-monophosphate (Gyulai et al., 1984; Kato et al., 1998). The choline resonance obtained at 3.6 ppm with proton (H^1) MRS arises from phosphocholine and glycerophosphocholine (Kato et al., 1998). Consistent

Table 2
Overall results of the separate meta-analyses performed for each of the study questions

Comparison	Number of studies	Random effects Z	Pooled effect size	P	95% Confidence interval
PME, euthymic vs. control	6	2.46	−0.83	0.014	−1.48, −0.17
PME, euthymic vs. control	5	2.00	−0.82	0.046	−1.63, −0.02
PME, depression vs. euthymic	3	3.47	0.86	0.0005	0.38, 1.35
PME, depression vs. control	3	0.69	0.15	0.488	−0.27, 0.54
PME, depression vs. euthymic	2	2.52	0.73	0.01	0.16, 1.29
PME, depression vs. control	2	1.06	0.25	0.29	−0.21, 0.72
PME, manic vs. euthymic	3	1.16	1.85	0.247	−1.28, 4.97
PME, manic vs. control	3	1.06	1.03	0.288	−0.87, 2.93
PME, manic vs. euthymic	2	0.52	0.42	0.60	−1.16, 2.00
PME, manic vs. control	2	0.46	0.16	0.65	−0.54, 0.86
PDE, euthymic vs. control	4	0.57	0.17	0.597	−0.40, 0.73

with the present results in bipolar depression, Moore et al. (2000) showed an increased anterior cingulate H^1 MRS choline resonance area in bipolar depression, which improved with antidepressant treatment and euthymia. Thus, an increased level of PME in bipolar depression is consistent with an increase in phosphocholine levels, as well as a possible increase of inositol phosphate levels.

In bipolar mania, our analysis failed to show any significant alterations of PME resonance areas. However, at least two reports suggest an increase in the PME resonance area in bipolar patients in the manic state compared to the PME resonance area in the euthymic state (Kato et al., 1991, 1993). Further studies will be necessary to clarify the matter.

A possible limitation of our study arises from the fact that we pooled data from different brain regions. However, studies from which data are pooled have evaluated the frontal lobe (Kato et al., 1991, 1992, 1993, 1994a,b, 1995; Deicken et al., 1995a) and temporal lobe (Deicken et al., 1995b) as regions of interest, and data from func-

Table 3
Effect sizes of the studies that are meta-analyzed to compare *PDE* levels of euthymic bipolar patients and healthy controls

Study	*PDE* Control	*N* Control	Age Mean ± S.D.	*PDE* Bip. euthymic	*N* Bip. euthymic	Age Mean ± S.D.	g	Weight
Deicken et al., 1995a	28.1 ± 3.8	14	39.8 ± 10.2	25.8 ± 3.6	12	40.1 ± 8.3	−0.62	2.94
Deicken et al., 1995b	27.1 ± 3.7	16	39.9 ± 11.1	29.8 ± 3.1	12	40.3 ± 8.7	0.78	2.99
Kato et al., 1992	19.7 ± 1.9	10	40.8 ± 9.1	20.2 ± 3.4	10	41.9 ± 8.4	0.18	2.64
Kato et al., 1993	20.1 ± 2.3	17	39.1 ± 10.1	20.9 ± 3.1	17	40.1 ± 10.8	0.29	3.37

Table 4
The comparison of the PME levels of depressed and euthymic bipolar patients

Study	*PME* Bip. euthymic	*N* Bip. euthymic	Age Mean ± S.D.	*PME* Bip. depressed	*N* Bip. depressed	Age Mean ± S.D.	*g*	Weight
Kato et al., 1992*	9.4 ± 1.7	10	41.9 ± 8.4	11.8 ± 2.1	10	42.0 ± 8.6	1.26	4.18
Kato et al., 1995	11.2 ± 2.5	17	40.4 ± 9.2	12.7 ± 3.2	11	38.6 ± 10.0	0.54	6.46
Kato et al., 1994b	9.6 ± 1.7	12	44.0 ± 9.7	11.3 ± 1.9	13	42.2 ± 9.7	0.94	5.62

*Data reanalyzed by dropping this study as there was some degree of overlap in subjects.

tional and structural neuroimaging studies are compatible with frontal and temporal lobe involvement in bipolar disorder (Hauser et al., 1989; Altshuler et al., 1991; George et al., 1993; Migliorelli et al., 1993; Soares et al., 1996). For the three studies which only provided lateralized data (Deicken et al., 1995a,b; Kato et al., 1995), we consistently used data from the right hemisphere. To run the meta-analysis, we had to use only one set of data from a single study and right hemisphere involvement may be more likely than left hemisphere involvement in bipolar disorder, if there is any lateralization of the disease process (Cummings and Mendez, 1984; Starkstein et al., 1987, 1991). Considering the variation caused by study procedures (including brain regions, acquisition parameters, etc.) that is reflected in our *Q* statistics, we used random effects models.

With regard to the specificity of these findings, low PME levels accompanied by high PDE levels have been observed in the frontal lobes of schizophrenic patients (Pettegrew et al., 1991). However, the pattern of phospholipid abnormalities in bipolar disorder patients appears to be different for the following reasons:

1. Low PME levels in euthymic bipolar patients have been observed in temporal lobes as well as in frontal lobes, while no significant alteration of temporal lobe PME levels has been reported in chronic schizophrenia patients (O'Callaghan et al., 1991; Calabrese et al., 1992; Deicken et al., 1994).
2. PDE levels do not appear to be altered in bipolar patients, whereas they have consistently been shown to be altered in schizophrenic patients (Pettegrew et al., 1991; Williamson et al., 1991; Shioiri et al., 1997; Volz et al., 1998b).

In terms of unipolar vs. bipolar affective illness, data regarding PME alterations in unipolar depression are inconsistent (Kato et al., 1992; Volz et al., 1998a). Volz et al. (1998a) reported increased PME values in the frontal lobes of patients with unipolar depression compared to healthy controls. However, Kato et al. (1992) compared PME values in depressed unipolar patients to those in euthymic unipolar patients and also to those in healthy controls. They failed to detect any significant alteration of PME values

Table 5
Comparison of the PME levels of manic and euthymic bipolar patients

Study	*PME* Bip. euthymic	*N* Bip. euthymic	Age Mean ± S.D.	*PME* Bip. manic	*N* Bip. manic	Age Mean ± S.D.	*g*	Weight
Kato et al., 1993	10.2 ± 1.5	17	40.1 ± 10.8	12.3 ± 1.9	17	40.1 ± 10.8	1.23	0.14
Kato et al., 1991*	9.0 ± 1.0	9	44.1 ± 9.1	14.0 ± 1.0	9	40.9 ± 12.9	5.00	0.12
Kato et al., 1995	11.2 ± 2.5	17	40.4 ± 9.2	10.3 ± 2.0	12	39.5 ± 7.4	−0.39	0.14

*Data reanalyzed by dropping this study as there was some degree of overlap in subjects.

in unipolar depression either in the depressive or in the euthymic state. Kato et al. (1994a) have hypothesized that the observed reductions in PME levels of euthymic bipolar patients might be a non-specific finding in brain disorders accompanied by atrophy. However, they did not observe any correlation between PME levels and ventricular enlargement in 39 bipolar euthymic patients. In addition, no correlation between PME resonance intensities and duration of illness could be detected (Kato et al., 1994a, 1998).

However, before attributing any etiologic relevance to the alteration of PME in bipolar illness, the possible confounding effect of medication status has to be considered. This is especially important given the circumstances where all findings come from samples where most patients were medicated or off medications for very short periods of time.

There are three possibilities:

1. The present findings may be a consequence of adaptive changes created by long-term lithium administration; if so, such an effect would influence all the reported data since patients were either on medications or off for only a period of 1 week (see review by Hyman and Nestler, 1996).
2. The present findings may solely reflect a trait- and/or state-dependent alteration of the membrane phospholipid metabolism in bipolar illness.
3. The present findings may be partly attributed to disease itself but also partly attributed to medications, rather than as a consequence of either one or the other.

If the first assumption is correct, low PME levels in the euthymic and high PME levels in the depressive states of bipolar patients are the reflections of lithium's long-term pharmacologic effects. Even in this case, the findings may still be relevant to the pathophysiology of bipolar illness. The PME resonance has contributions from inositol-1-monophosphate (Gyulai et al., 1984; Kato et al., 1998). Shamir et al. (1998) have reported that cell lines from bipolar patients have significantly lower inositol monophosphatase (IMPase) activity than cell lines from control subjects. Moreover, among bipolar patients, lithium responders exhibited significantly lower IMPase activity compared to non-responders (Shamir et al., 1998). Lithium has been demonstrated to inhibit the enzyme IMPase (Renshaw et al., 1986b) and increase PME in in-vivo human brain (Yildiz et al., 2001). It is a heuristic hypothesis that bipolar subjects exhibit genetically determined low IMPase activity and that lithium, by causing more inhibition of the enzyme activity, may cause an increase in inositol 1-monophosphate and/or a decrease in free inositol beyond a critical point which stimulates a compensatory transcriptional up-regulation of the enzyme's synthesis. It has been shown that chronic lithium administration causes an increase in IMPase and its messenger RNA levels (Renshaw et al., 1986a; Shamir et al., 1998). When IMPase activity is increased, a bipolar patient's clinical status might be stabilized in a euthymic state, and inositol 1-monophosphate levels would be decreased, as would PME levels. Whenever the compensatory up-regulating effect of lithium on the enzyme IMPase was lost, the patient's clinical status would be destabilized and the patient would have an episode of altered mood state. In that case, since the enzyme was less active again, inositol 1-monophosphate levels and PME levels would go up. The present findings are compatible with this hypothesis for the eythymic and for the depressed states, but not for the manic state. This may be a reflection of the inconsistency of the available data (Kato et al., 1991, 1993, 1995) and/or the small number of studies included in the meta-analysis of the PME values in manic patients.

However, the second possible scenario assumes that the present findings do not reflect alterations caused by lithium or other psychotrophic medications. This assumption is supported by the following evidence:

1. Deicken et al. (1995a,b) found no significant difference in PME and PDE values between seven patients who had been taking lithium and five patients who were not treated with lithium.
2. Reduced frontal lobe PME has been reported

in a group of 10 euthymic bipolar patients, seven of whom had not been treated with lithium (Kato et al., 1992).
3. Kato et al. (1993) found no correlation of PME peak areas to brain lithium concentrations.
4. When the effect of drug administration was examined in 25 bipolar patients in a depressive state, there was no significant difference in the PME levels between the medicated ($n = 12$) and drug-free ($n = 13$) patients (Kato et al., 1994b).
5. Kato et al. (1994a) found no differences in PME levels between those patients treated with antipsychotics and those without antipsychotics.

The correct interpretation is uncertain and future studies of drug-naive bipolar patients in different mood states will be required to provide a more complete perspective. However, in either case, the results of these meta-analyses suggest that altered frontal and temporal lobe PME in bipolar illness represents a trait- and also possibly a state-dependent abnormality of membrane phospholipid metabolism. This is in accordance with the trait-dependent abnormality of membrane molecular dynamics in red blood cells of bipolar patients (Pettegrew et al., 1993). Reports which document a hyperactive platelet phosphatidylinositol pathway in bipolar manic patients (Brown et al., 1993; Friedman et al., 1993), altered membrane integrity in mood disorders (as examined by indices of erythrocyte membrane structure and function) (Pettegrew et al., 1982; Meltzer, 1991) and increased content of a structurally important protein (ankyrin) in erythrocyte membranes of bipolar patients (Zhang and Meltzer, 1989) also suggest membrane phospholipid abnormalities and may parallel a dysregulation in brain signal transduction mechanisms of relevance in the pathophysiology of bipolar illness.

In conclusion, while this study is limited due to the paucity of available data for a comprehensive meta-analysis, it serves to summarize the available literature and suggests trait-dependent alterations of PME levels in bipolar illness. Given the cost and technical difficulties of the MRS experiments resulting in limited sample sizes for typical studies, individual data should be provided in future reports to enable more extensive meta-analyses. Future improvements in the sensitivity and resolution of ^{31}P MRS, as provided by increased field strength scanners, will hopefully enable more specific identification of the particular metabolite or metabolites altered in bipolar illness. These, together with the exploration of current findings in medication-free unipolar and bipolar affective disorder patients in different mood states, will provide important insights to our understanding of this complex illness.

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