Eur Arch Psychiatry Clin Neurosci (1998) 248 : 301–306

ORIGINAL PAPER

Tadafumi Kato · Jun Murashita · Atsushi Kamiya
Toshiki Shioiri · Nobumasa Kato · Toshiro Inubushi

Decreased brain intracellular pH measured by ^{31}P-MRS in bipolar disorder: a confirmation in drug-free patients and correlation with white matter hyperintensity

Received: 7 January 1998 / Accepted: 15 September 1998

Abstract The authors have previously reported decreased intracellular pH (pHi) in the frontal lobes in euthymic bipolar patients treated with lithium using ^{31}P-MRS. White matter hyperintensity (WMHI) is frequently seen in bipolar disorder. To examine a possible effect of lithium on pHi and the relationship between pHi and WMHI, seven drug-free euthymic bipolar patients were examined, and T_2-weighted MRI were examined in 14 previously reported bipolar patients. Drug-free patients showed significantly lower pHi than controls. WMHI was associated with low pHi and increased phosphodiester peak. These results suggest that decrease of pHi is not an effect of lithium but is instead related to the pathophysiology of illness. Decrease of pHi and increase of the PDE peak may be the biochemical basis of WMHI in bipolar disorder.

Key words. Bipolar affective disorder · Phosphorus-31 magnetic resonance spectroscopy · Magnetic resonance imaging · Mood disorder

Introduction

Brain phosphorus metabolism in patients with bipolar disorder has been investigated using phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) [11, 12, 15–20]. These studies have indicated (a) alteration of the phosphomonoester (PME) peak in the frontal [11, 15, 17, 19] and temporal lobes [12], (b) decrease of phosphocreatine (PCr) predominantly in the left frontal lobe [16, 18, 20], (c) decreased intracellular pH (pHi) in the frontal lobes [17, 19], and (d) increase of the phosphodiester (PDE) peak in the frontal lobes [11].

The finding that pHi was decreased in euthymic patients with bipolar disorder compared with normal controls is particularly intriguing. The 0.05 unit difference in pHi seems to be a notable finding, given that pHi is strictly regulated in the brain. In schizophrenia, moreover, although changes in PME and PDE have been widely reported, decreases in pHi have never been observed, suggesting that pHi changes may be a potential clue in understanding the pathophysiology of bipolar disorder.

However, the following questions should be addressed:

1. Is the decrease in pHi a result of lithium treatment? All the bipolar patients examined in our previous study were treated with lithium [17, 19]. Although effects of lithium on pHi have not been reported thus far, it cannot be ruled out that lithium may affect pHi through the alteration of Na^+/H^+ exchanger activity [2].

2. Is this finding related to the white matter hyperintensity (WMHI) observed by T_2-weighted magnetic resonance imaging (MRI)? Recent MRI studies on bipolar disorder consistently noted that deep white matter hyperintensity (DWMHI) and periventricular hyperintensity (PVH) are more frequently seen in bipolar patients than in age-matched normal controls [1]. On the other hand, it was reported that WMHI is associated with decreased ATP levels, decreased pHi [32] and PME levels [10]. Of these findings in elderly patients, low pHi and decreased PME are the same findings as those observed in bipolar disorder. It seems possible, therefore, that there is a correlation between low pHi and WMHI.

In this study, drug-free patients with bipolar disorder were examined by ^{31}P-MRS to elucidate whether or not a decrease in pHi in the brain is also observed in these patients, and previously reported ^{31}P-MRS data were reanalyzed in light of existence or absence of WMHI detected by T_2-weighted MRI.

T. Kato (✉)
Department of Neuropsychiatry, Faculty of Medicine,
University of Tokyo, Hongo 7–3-1, Bunkyo, Tokyo,
113-8655, Japan

T. Kato · J. Murashita · A. Kamiya · T. Shioiri · N. Kato
Department of Psychiatry, Shiga University of Medical Science,
Otsu, Japan

T. Inubushi
Molecular Neurobiology Research Center,
Shiga University of Medical Science, Otsu, Japan

Subjects and methods

Study 1: Drug-free patients

Seven patients with bipolar disorder (seven men and two women; mean age 44.1 ± 16.9 years) were examined for drug-free study. Four of them had DSM-III-R bipolar-I disorder and three had bipolar-II disorder (Table 1). It was confirmed through an interview by a senior psychiatrist that they were in the euthymic state and had no mood symptoms over the 2 weeks prior to MRS examination. None of the patients had been administered drugs of any kind for at least 10 days (11–365 days, mean 103 days) prior to examination. Six patients had been receiving lithium monotherapy before the drug-free period. The remaining subject (case 7) had been treated with trazodone and sulpiride but never with lithium. They did not have any neurological disorders, major medical disease, or substance abuse. They did not have major structural abnormalities detected by T_1-weighted MRI. Five of these patients had dropped out of treatment in the outpatient clinic and were asked to join this study by mail. In one patient, lithium had been stopped by an attendant physician due to side effects. In the remaining patient (case 7), an attendant physician had stopped drugs in order to perform light therapy.

The results in these seven patients were compared with previously reported data for 60 normal control subjects [19]. There were no significant age differences between the seven patients and controls. The data in the seven drug-free patients were collected during the same period as with the controls, because they were gradually collected during the course of this study.

Study 2: Relationship between MRI and ^{31}P-MRS

Of the 40 patients treated with lithium in our previous report [19], only 13 patients had been examined by T_2-weighted MRI for clinical purpose. Similarly, T_2-weighted MRI was available in only one of seven patients in the drug-free study. A total of 14 patients were examined.

All subjects provided informed written consent before participating in the study.

Magnetic resonance spectroscopy (studies 1 and 2)

The method of MRS data acquisition and its reliability have been described in our previous report [19]. Briefly, subjects were examined on a 1.5-T Signa MR system (GE Medical Systems, Milwaukee, Wis.) equipped with a spectroscopy package. Surface coils for ^{1}H and ^{31}P (GE Medical Systems) were placed over the subject's head. The volume of interest was the 30-mm slice between the front pole and the front edge of the corpus callosum parallel to the coil [17]. ^{31}P-MR spectra were obtained using depth-resolved surface coil spectroscopy (DRESS) [3]. The repetition time (TR) was set at 3 s. One hundred twenty-eight scans were averaged. The number of data points was 1024 and receiver band width was 4000 Hz.

FIDs were processed using a GE 1280 DATA station (GE Medical Systems, Milwaukee, Wis.). Broad peaks and baseline distortion were canceled using the convolution difference method [6]. After Fourier transformation, baseline correction was applied to the phase-corrected spectra (Fig. 1). Peak areas were calculated by manual curve fitting. Metabolite data were shown as peak area percent to the total phosphorus signal. Intracellular pH was calculated from the difference of chemical shifts between inorganic phosphate and phosphocreatine [24]. Inter-assay intra-individual coefficients of variation (CV) of peak area percentages were less than 10%, except for Pi peak, and CVs of pHi was 0.80% [18, 19].

Magnetic resonance imaging (study 2)

Magnetic resonance images were also obtained using a Signa (GE Medical Systems, Milwaukee, Wis.) 1.5-Tesla MR system in a session independent from that using ^{31}P-MRS. Subjects lay with their orbitomeatal (OM) line vertical to the stretcher. After scout sagittal images were obtained, T_2-weighted and proton-density-weighted double spin-echo axial images were taken with a field of view (FOV) of 24 cm, a slice thickness of 5 mm with an inter-scan gap of 2.5 mm, a 256 × 256 matrix, a repetition time (TR) of 2000 ms, echo times (TE) of 80 ms and 20 ms, respectively, and a number of excitations (NEX) of 2. T_1-weighted axial images were also obtained with TR of 500 ms and TE of 20 ms.

These MRI films were first qualitatively inspected by a neuroradiologist, then quantitatively scored by two neuropsychiatrists.

Table 1 Phosphorus-31 magnetic resonance spectrum in drug-free patients with bipolar disorder (*PME* phosphomonoester; *Pi* inorganic phosphate; *PDE* phosphodiester; *PCr* phosphocreatine; *ATP* adenosine triphosphate)

Diagnosis	Case no.	Subtype	Age	No. of subjects	Sex	Drug-free period [days]	pH	Peak area [%]				
								PME	Pi	PDE	PCr	β-ATP
Bipolar disorder (Drug-free)	1	BPI	43		M	30	6.99	7.9	5.9	16.8	12.1	20.1
	2	BPI	42		F	132	6.99	11.6	6.1	22.6	15.0	12.8
	3	BPI	66		M	365	7.04	13.9	6.9	19.0	14.3	13.4
	4	BPI	35		F	120	7.02	12.8	3.1	26.3	12.9	12.1
	5	BPII	68		F	11	7.04	9.4	9.7	17.2	14.7	13.6
	6	BPII	24		F	41	7.00	9.7	6.7	22.0	12.7	12.8
	7	BPII	31		M	28	7.03	13.7	3.2	16.6	10.2	14.2
		Mean	44.1	7	(4F, 3M)	103.8	7.01*	11.3	5.9	20.1	13.1	14.1
		SD	16.9			124.5	0.02	2.3	2.3	3.5	1.6	2.7
Bipolar disorder[a] (on Lithium)		Mean	42.0	40	(24F, 16M)		7.01	10.6	5.7	20.7	13.4	13.5
		SD	12.4				0.04	1.7	1.5	2.9	1.9	1.9
Controls[a]		Mean	39.6	60	(33F, 27M)		7.05	11.2	6.0	20.1	13.5	13.6
		SD	13.9				0.04	1.5	1.3	2.5	1.5	1.9

[a] Cited from Kato et al (1994)

* $p < 0.05$ to controls by Mann-Whitney U-test

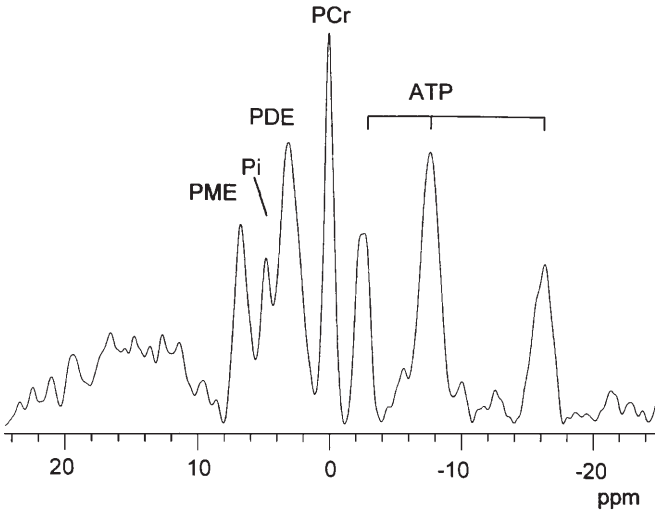

Fig. 1. Phosphorus-31 magnetic resonance spectrum in the frontal lobes in a normal control subject

The PVH and DWMHI was scored by T_2-weighted MR images using the four-point scale [8]. Representative images were prepared for these four-point scales, and all images were compared with these images. The scoring was performed blindly to the ^{31}P-MRS findings of the subjects. The two scores (PVH and DWMHI) were summed to yield a total WMHI score. Patients having WMHI scores of 1 or more were regarded as having WMHI.

Statistical analysis

Two-way analysis of covariance (2-way ANCOVA), Spearman's coefficient of correlation, and Mann-Whitney U-test were used for statistical analysis.

Results

Study 1: Drug-free patients

The results of the drug-free study are summarized in Table 1. Intracellular pH was significantly lower in drug-free bipolar patients compared with that in 60 normal controls (U = 111, $p < 0.05$ by two-tailed Mann-Whitney U-test). There was no significant difference in the PME peak area between drug-free bipolar patients and controls. Also, there was no significant difference in other peak area ratios between these two groups.

Study 2: Relationship between MRI and ^{31}P-MRS

Eight of 14 patients were judged as having WMHI. These 8 patients had an average WMHI score of 2.7 ± 2.2. The WMHI score was significantly correlated with age (r = 0.71, $p < 0.01$) and with PDE peak area (r = 0.56, $p < 0.05$; Fig. 2).

Bipolar patients with WMHI tended to have lower pHi (7.02 ± 0.03; p = 0.10) compared with normal controls (7.05 ± 0.04), whereas bipolar patients without WMHI did not differ from controls (7.05 ± 0.03; Table 2). Because bipolar patients with WMHI were significantly older than the controls (51.1 ± 12.9 years), the data in these patients were compared with elderly controls more than 35 years old who were selected from the 60 controls (n = 33; age 50.3 ± 9.0 years). When compared with elderly controls (7.05 ± 0.04), the difference was close to significance (p = 0.06).

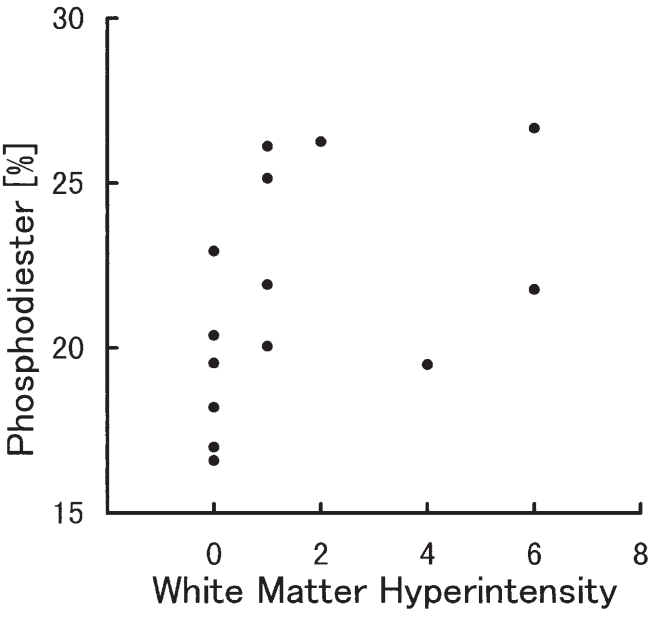

Fig. 2. Relationship between white matter hyperintensity scores by T_2-weighted MRI and phosphodiester peak area by ^{31}P-MRS in patients with bipolar disorder. Statistically significant correlation was found (r = 0.56, $p < 0.05$)

To further examine the relationship between ^{31}P-MRS findings and WMHI, two-way ANCOVA with factors of diagnosis (bipolar with WMHI, bipolar without WMHI, controls), gender, and covariate of age was applied. The factor of age was found to be significant only for PCr (F = 10.0, $p < 0.005$), whereas that of diagnosis was found to be significant only for the PDE peak (F = 6.4, $p < 0.005$). The PDE peak area percent was significantly higher in the bipolar disorder patients with WMHI (23.4 ± 2.9) compared with 60 controls (20.1 ± 3.6; $p < 0.01$) and patients without WMHI (19.1 ± 2.3; $p < 0.05$). This result did not change even when it was compared with 33 elderly controls (20.0 ± 2.8; $p < 0.005$).

Discussion

Study 1: Drug-free patients

We found significantly decreased pHi in the brains of drug-free patients with bipolar disorder compared with normal controls. This result suggests that the decrease in pHi in the brain in euthymic patients with bipolar disorder found in our previous study [17, 19] may be related to pathophysiology of bipolar disorder rather than to the ef-

Table 2 Relationship between phosphorus-31 magnetic resonance spectrum findings and subcortical hyperintensity observed by T_2-weighted MRI (*F* female; *M* male; *PME* phosphomonoester; *PDE* phosphodiester)

	No. of subjects	Sex	Age [years] mean ± SD	pH mean ± SD	PME [%] means ± SD	PDE [%] mean ± SD
Bipolar disorder (WMHI +)	8	(5F, 3M)	51.1 ± 12.9	7.02 ± 0.03*	10.8 ± 2.0	23.4 ± 2.9**
Bipolar disorder (WHMI –)	6	(2F, 4M)	33.6 ± 11.0	7.05 ± 0.03	11.4 ± 1.6	19.1 ± 2.3
Controls[a]	60	(33F, 27M)	39.6 ± 13.9	7.05 ± 0.04	11.2 ± 1.5	20.1 ± 2.5
Elderly controls[a]	33	(22F, 11M)	50.3 ± 9.0	7.05 ± 0.04	11.2 ± 1.7	20.0 ± 2.8

[a] From Kato et al. (1994)
* $p = 0.06$ for elderly controls using Mann-Whitney U-test
** $p < 0.001$ for elderly controls using Mann-Whitney U-tes

fects of lithium. In contrast to the present study, Deicken et al. [11, 12] found no difference in pHi either in the frontal or temporal lobes between drug-free patients with bipolar disorder and normal controls, using magnetic resonance spectroscopic imaging. However, the standard deviation of pHi in their study (0.06–0.28) was much higher than that in our study (0.01–0.04), which might have obscured the difference.

In contrast to the studies by Deicken et al. who reported a decrease in the PME peak in bipolar patients who were drug-free for 7 days [11, 12], no decrease in PME level was found in this study. In this study the drug-free period was more than 28 days in six of seven subjects, which we regarded as sufficient to exclude any effects of lithium. On the other hand, the wash-out period in the studies by Deicken et al. may not be enough to exclude a possible effect of lithium. Although the elimination half-life of lithium detected by ^{7}Li-MRS in the human brain had been assumed to be approximately 2 days [30], it was calculated to be much longer in an animal experiment [27]. There are also many technical differences between these two studies, which might have caused this discrepancy. Deicken et al. used a head coil and magnetic resonance spectroscopic imaging technique, whereas we used a surface coil and the DRESS method; therefore, the regions examined were not completely the same between these two studies.

There are only few studies of effects of lithium on brain phosphorus metabolism. Renshaw et al. [28, 29] and Preece et al. [26] examined effects of lithium on brain phosphorus metabolism in experimental animals, and found increase of the PME peak 1 week after the initiation of lithium treatment. After the initial increase, the PME peak decreased to the normal levels. Silverstone et al. [31] found that brain phosphorus metabolism was not altered after lithium treatment for 1 week in human volunteers. Keshavan et al. [21] examined effects on lithium on brain phosphorus metabolism in patients with schizophrenia after 2-week lithium treatment. None of these researchers found a decrease in intracellular pH after lithium treatment. There is no report on effects of long-term lithium treatment for more than 1 month, comparable to the clinical situation in bipolar disorder; therefore, it cannot be ruled out that long-term lithium treatment may decrease the PME peak. However, we cannot draw a definite conclusion because the number of subjects were very small, mixed with bipolar I and bipolar II, and the standard deviation in PME in the patients was somewhat large.

Study 2: Relationship between MRI and ^{31}P-MRS

A decrease in pHi was not found in bipolar patients without WMHI but was found in patients having WMHI (Table 2). Moreover, we also found – unexpectedly – that the PDE peak area was significantly higher in patients with WMHI than in those without WMHI or age-matched controls (Fig. 2; Table 2). Although we did not find increase of the PDE peak in bipolar disorder, Deicken et al. [11] reported a significant increase in PDE peak in the frontal lobes of patients with bipolar disorder. These findings suggest a possible close correlation between three independent findings in neuroimaging studies in bipolar disorder, i.e., between high frequency of WMHI by MRI, decrease in pHi and increase in the PDE peak by ^{31}P-MRS.

What is the causal relationship of these parameters? To date, there have been no histopathological studies in the postmortem brains of patients with both bipolar disorder and WMHI. Among the general population, WMHI has been associated with myelin pallor and dilatation of the perivascular space [7, 13]. These findings are thought to be the results of ischemic changes. Although it is not known whether the finding in bipolar disorder is histopathologically the same as that observed in normal elderly people, WMHI in bipolar disorder may also be associated with ischemia.

Sappey-Marinier et al. [32] examined the WMHI areas in elderly subjects using ^{31}P-MRS, and found both a significant decrease in β-ATP and a non-significant trend of low pHi. In their subsequent study, however, only a decrease in PME peak was noted [10]. An increase in PDE peak has never been reported in WMHI of elderly normal subjects. Therefore, it is possible that WMHI in bipolar disorder may be the result of a different mechanism than WMHI in normal elderly subjects. In fact, it has been reported that ^{1}H-MRS findings are different between the WMHI region in Alzheimer's disease and that in vascular dementia [9].

In this study most of the patients had only slight WMHI, i.e., scores of 1–2, which were much milder than

the cases in the study of ^{31}P-MRS in WMHI in normal elderly subjects [10, 32]. In our patients with WMHI, most of the white matter region appeared normal; therefore, the decrease in pHi and increase in the PDE peak cannot reflect the biochemical properties of the WMHI tissues themselves, but must reflect the metabolism in normal-appearing white matter. We should thus assume that some biochemical process accompanying the decrease in pHi and increase in PDE causes WMHI.

To our knowledge, a decrease in pHi has only been reported in a few pathological states in the human brain, i.e., WMHI [32], acute stroke [34], and subarachnoid hemorrhage [4], all of which reflect ischemic insult. While decrease in pHi in WMHI (7.02) is comparable to bipolar disorder, that in other diseases is much larger (6.90) than bipolar disorder.

Implications for pathophysiology of bipolar disorder

In bipolar disorder, pHi decrease might be caused by an accumulation of lactate due to ischemia, or decreased activity of the Na^+/H^+ exchanger. Lactate accumulation has never been found either in the subcortical region [14] or the frontal lobes (H. Hamakawa et al., unpublished data) in euthymic patients with bipolar disorder using ^{1}H-MRS. The Na^+/H^+ exchanger (NHE) is a main determinant of pHi in neuronal cells [33]. It was reported that the Na^+/Li^+ counter transport activity was decreased in red blood cells of patients with bipolar disorder, although it is still controversial [23]. Recently, it has been determined that Na^+/Li^+ counter transport activity is mediated by the Na^+/H^+ exchanger isoform 1 (NHE-1) in NHE-1 cDNA-injected oocytes [5]; therefore, it is possible that dysfunction of NHE-1 may be responsible for these findings in bipolar disorder.

The PDE peak originates mainly from the membrane phospholipid itself [22]. It also includes signals from soluble membrane degenerating products, such as glycerophosphocholine or glycero-phosphoethanolamine. The observed large increase in PDE peak area might be caused by prolongation of the T_2 relaxation time of membrane phospholipid molecules due to increased mobility, or accumulation of membrane degenerating products.

Limitations

The major limitation of this study is the small number of subjects mixed with bipolar-I and bipolar-II cases, which limits the generalization of this finding. However, it is not easy to recruit drug-free euthymic patients with bipolar disorder in a clinical situation. Before maintenance treatment, these patients are generally not diagnosed as having bipolar disorder, and by the time the patients diagnosed as having bipolar disorder become euthymic, they are generally receiving maintenance treatment. It is not ethically approved to stop lithium treatment for research purposes, since such termination may induce relapse or treatment-resistant rapid cycling [25]; therefore, we looked for bipolar patients who had dropped out of lithium treatment of their own accord, which limited the number of subjects for recruitment. We did not select only bipolar-I or bipolar-II cases, because the decrease in pHi has been observed in both of these disorders [19]. We must also consider that the drug-free patients who dropped out of lithium treatment may not be representative of bipolar disorder on the whole. Therefore, a larger and more homogeneous group would be required to fully validate the findings in this study.

It should be noted that, in this study, the ^{31}P-MRS results were obtained over a relatively large region that included many kinds of tissues, such as gray matter, normal appearing white matter, a white matter hyperintensity region, muscles, skin and cerebrospinal fluid. Although it is necessary to locate the VOI of ^{31}P-MRS to the WMHI region only, this is not easily done, since the minimum measurable volume of ^{31}P-MRS is approximately 27 cm^3. In this study T_2-weighted MRI was not obtained in normal controls. It would be required to see the relationship between WMHI and intracellular pH in other diagnostic groups in the future. Because WMHI was scored based on the MRI films of 5-mm-thick and 2.5-mm inter-scan gap, small WMHI might have been dismissed. There are many other factors to be taken into consideration in interpreting ^{31}P-MRS data, as we discussed in our previous study [19].

Despite these limitations, this is the first report to confirm decreased intracellular pH in drug-free bipolar patients and to reveal a possible biochemical background of WMHI in bipolar disorder.

Acknowledgements This study was supported by a Research Grant for Nervous and Mental Disorders from the Japanese Ministry of Health and Welfare (8B-2), and a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education (no. 09770738).

References

1. Altshuler LL, Curran JG, Hauser P, et al. (1995) T_2 hyperintensities in bipolar disorder: magnetic resonance imaging comparison and literature meta-analysis. Am J Psychiatry 152:1139–1144
2. Bitran JA, Potter WZ, Manji HK, et al. (1990) Chronic Li^+ attenuates agonist- and phorbol ester-mediated Na^+/H^+ antiport activity in HL-60 cells. Eur J Pharmacol 188:193–202
3. Bottomley PA, Foster TB, Darrow RD, et al. (1984) Depth-resolved surface-coil spectroscopy (DRESS) for in vivo ^{1}H, ^{31}P and ^{13}C NMR. J Magn Reson 59:338–342
4. Brooke NS, Ouwerkerk R, Adams CB, et al. (1994) Phosphorus-31 magnetic resonance spectra reveal prolonged intracellular acidosis in the brain following subarachnoid hemorrhage. Proc Natl Acad Sci USA 91:1903–1907
5. Busch S, Burckhardt BC, Siffert W (1995) Expression of the human sodium/proton exchanger NHE-1 in Xenopus laevis oocytes enhances sodium/proton exchange activity and establishes sodium/lithium counter transport. Eur J Physiol 429:859–869
6. Champbell ID, Dobson CM, Williams RJP, et al. (1973) Resolution enhancement of protein PMR spectra using the difference between a broadened and a normal spectrum. J Magn Reson 11:172–181

7. Chimowitz MI, Estes ML, Furlan AJ, et al. (1992) Further observations on the pathology of subcortical lesions identified on magnetic resonance imaging. Arch Neurol 49:747–752
8. Coffey CE, Fiegel GS, Djang WT, et al. (1989) White matter hyperintensity on magnetic resonance imaging: clinical and neuroanatomic correlates in the depressed elderly. J Neuropsychiatry Clin Neurosci 1:135–144
9. Constans JM, Meyerhoff DJ, Gerson J, et al. (1995) H-1 MR spectroscopic imaging of white matter signal hyperintensities: Alzheimer disorder and ischemic vascular dementia. Radiology 197:517–523
10. Constans JM, Meyerhoff DJ, Norman D, et al. (1995) ^{1}H and ^{31}P magnetic resonance spectroscopic imaging of white matter signal hyperintensity areas in elderly subjects. Neuroradiology 37:615–623
11. Deicken RF, Fein G, Weiner MW (1995) Abnormal frontal lobe phosphorus metabolism in bipolar disorder. Am J Psychiatry 152:915–918
12. Deicken DF, Weiner MW, Fein G (1995) Decreased temporal lobe phosphomonoesters in bipolar disorder. J Affect Disord 33:195–199
13. Fazekas F, Kleinert R, Offenbacher, et al. (1991) The morphologic correlate of incidental punctuate white matter hyperintensities on MR images. Am J Neuroradiol 12:915–921
14. Hamakawa H, Kato T, Shioiri T, et al. (in press) Proton magnetic resonance spectroscopy of the basal ganglia in patients with affective disorders. Eur Arch Psychiatry Neurosci
15. Kato T, Shioiri T, Takahashi S, et al. (1991) Measurement of phosphoinositide metabolism in bipolar patients using in vivo ^{31}P-MRS. J Affect Disord 22:185–190
16. Kato T, Takahashi S, Shioiri T, et al. (1992) Brain phosphorous metabolism in depressive disorders detected by phosphorous-31 magnetic resonance spectroscopy. J Affect Disord 26: 223–230
17. Kato T, Takahashi S, Shioiri T, et al. (1993) Alterations in brain phosphorous metabolism in bipolar disorder detected by in vivo ^{31}P and ^{7}Li magnetic resonance spectroscopy. J Affect Disord 27:53–60
18. Kato T, Takahashi S, Shioiri T, et al. (1994) Reduction of brain phosphocreatine in bipolar II disorder detected by phosphorus-31 magnetic resonance spectroscopy. J Affect Disord 31: 125–133
19. Kato T, Shioiri T, Murashita J, et al. (1994) Phosphorus-31 magnetic resonance spectroscopy and ventricular enlargement in bipolar disorder. Psychiatry Res Neuroimaging 55:41–50
20. Kato T, Shioiri T, Murashita J, et al. (1995) Lateralized abnormality of high energy phosphate metabolism in the frontal lobes of patients with bipolar disorder detected by phase-encoded ^{31}P-MRS. Psychol Med 25:557–566
21. Keshavan MS, Pettegrew JW, Panchlingam K (1995) MRS in the study of psychoses: psychopharmacological studies. In: Nasrallah HA, Pettegrew JW (eds) NMR spectroscopy in psychiatric brain disorders. American Psychiatric Press, Washington, DC, pp 131–146
22. Kilby PM, Bolas NM, Radda GK (1991) ^{31}P-NMR study of brain phospholipid structures in vivo. Biochim Biophys Acta 1085:257–264
23. Mota de Freitas DE, Espanol MT, Dorus E (1991) Lithium transport in red blood cells of bipolar patients. In: Gallicchio VS, Lexington KY (eds) Lithium therapy monographs, vol 4. Karger, Basel, pp 96–120
24. Petroff OAC, Prichard JW, Behar KS, et al. (1985) Cerebral intracellular pH by ^{31}P nuclear magnetic resonance spectroscopy. Neurology 35:781–788
25. Post RM, Leverich GS, Altshuler L, et al. (1992) Lithium-discontinuation-induced refractoriness: preliminary observations. Am J Psychiatry 149:1727–1729
26. Preece NE, Gadian DG, Houseman J, et al. (1992) Lithium-induced modulation of cerebral inositol phosphate metabolism in the rat. A multinuclear magnetic resonance study in vivo. Lithium 3:287–297
27. Ramaprasad S, Newton JEO, Cardwell D, et al. (1992) In vivo ^{7}Li NMR imaging and localized spectroscopy of rat brain. Magn Reson Med 25:308–318
28. Renshaw PF, Summers JJ, Renshaw CE, et al. (1986) Changes in the P-31 NMR spectra of cats receiving lithium chloride systemically. Biol Psychiatry 21:694–698
29. Renshaw PF, Schnall MD, Leigh JS Jr (1987) In vivo P-31 NMR spectroscopy of agonist-stimulated phosphatidylinositol metabolism in cat brain. Magn Reson Med 4:221–226
30. Renshaw PF, Wicklund S (1988) In vivo measurement of lithium in humans by nuclear magnetic resonance spectroscopy. Biol Psychiatry 23:465–356
31. Silverstone PH, Hanstock CC, Fabian J, et al. (1996) Chronic lithium does not alter human myo-inositol or phosphomonoester concentrations as measured by ^{1}H and ^{31}P MRS. Biol Psychiatry 40:235–246
32. Sappey-Marinier D, Deicken RF, Fein G, et al. (1992) Alterations in brain phosphorus metabolite concentrations associated with areas of high signal intensity in white matter at MR imaging. Radiology 183:247–256
33. Tolkovski AM, Richards CD (1987) Na^{+}/H^{+} exchange is the major mechanism of pH regulation in cultured sympathetic neurons: measurement in single cell bodies and neurites using a fluorescent pH indicator. Neuroscience 22:1093–1102
34. Vion-Dury J, Meyerhoff DJ, Cozzone PJ, et al. (1994) What might be the impact on neurobiology if the analysis of brain metabolism is by in vivo magnetic resonance spectroscopy? J Neurol 241:354–371