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ORIGINAL PAPER

Hiroshi Hamakawa · Tadafumi Kato · Jun Murashita
Nobumasa Kato

Quantitative proton magnetic resonance spectroscopy of the basal ganglia in patients with affective disorders

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Abstract Proton magnetic resonance spectra were recorded from a subcortical region containing the basal ganglia in 40 patients with affective disorders (18 with bipolar disorder and 22 with major depression) and in 20 normal controls. The absolute concentration of the choline-containing compounds (Cho) in the patients with bipolar disorder in the depressive state was significantly higher than that in the normal controls. The patients with bipolar disorder had significantly higher levels of the Cho/creatine + phosphocreatine (Cr) and Cho/N-acetyl-l-aspartate (NAA) peak ratio compared with the normal controls in both the depressive and euthymic states, with a tendency to higher levels in the depressive state. The Cho/NAA peak ratio was also significantly higher in the patients with major depression compared with the normal controls. These results suggest that the membrane phospholipid metabolism in the basal ganglia is altered in affective disorders.

Key words Mood disorder · Magnetic resonance spectroscopy · Basal ganglia · Bipolar disorder · Major depression · Choline-containing compounds · Brain imaging

Introduction

In vivo magnetic resonance spectroscopy (MRS) is a useful noninvasive means of observation of metabolites in the brain, and in particular ^{1}H-MRS and ^{31}P-MRS have been widely applied in clinical research. ^{1}H-MRS can detect several important metabolites such as N-acetyl-l-aspartate (NAA), choline-containing compounds (Cho), and creatine + phosphocreatine (Cr; Miller et al. 1991). Several findings have been brought to light in this field since Sharma et al. (1992) first applied this technique in bipolar disorder. These results have suggested that the Cho/Cr peak ratio in the subcortical region including the basal ganglia is elevated in patients with bipolar disorder in the euthymic state (Sharma et al. 1992; Lafer et al. 1994; Kato et al. 1996) and in these with major depression in the depressed state (Charles et al. 1993; Renshaw et al. 1994). On the other hand, Baxter et al. (1985) and Buchsbaum et al. (1986) reported decreased glucose metabolism in the basal ganglia in affective disorders, whereas Husain et al. (1991) and Krishnan et al. (1992) found decreased volume of basal ganglia. It is also reported that post-stroke depression is frequently associated with infarction in the basal ganglia (Starkstein et al. 1987; Krishnan and Figiel 1989). These results collectively suggest that the basal ganglia plays an important role in the pathophysiology of affective disorders.

There is no report about ^{1}H-MRS in bipolar depression, although state-dependent alteration of the Cho peak ratio in major depression has been reported (Charles et al. 1993; Renshaw et al. 1994). Therefore, it is important to examine whether increase of the Cho peak is specific to unipolar depression or is commonly observed in both unipolar and bipolar depression. Moreover, the previous evaluations were of changes in metabolite ratios, which made it difficult to assess quantitative change of the metabolites. In this study we examined the absolute concentrations of metabolites in the subcortical region including the basal ganglia by quantitative ^{1}H-MRS in 18 patients with bipolar disorder and 22 patients with major depression.

Subjects and methods

The subjects were patients hospitalized in the psychiatry ward of the Shiga University of Medical Science Hospital. All of them were right-handed. Eighteen of them had bipolar disorder (5 men and 13 women; age 45.8 ± 12.6 years) and 22 major depression (9 men and 13 women; age 49.4 ± 13.1 years). Eleven of the patients with bipolar disorder were examined in the depressive state, and 16 in the euthymic state. Eight patients with bipolar disorder were diagnosed as having bipolar disorder, and 10 as having bipolar disorder not otherwise specified (NOS; bipolar-II disorder). Nineteen

H. Hamakawa (✉) · T. Kato · J. Murashita · N. Kato
Department of Psychiatry, Shiga University of Medical Science, Seta Tsukinowacho, Otsu, Shiga, 520-21, Japan

Table 1 Characteristics of the patients. ALP alprazoram; AMT amitriptyline; CBZ carbamazepine; CLM clomipramine; CLX cloxazoram; DZP diazepam; HPD haloperidol; IMP imipramine; Li lithium carbonate; LP levomepromadine; MIA mianserin; SPD sulpiride; THZ thioridazine; TZN trazodone; VPA sodium valproate; ZP zotepine; HRSD score on the Hamilton Rating Scale for Depression

Bipolar disorder

Patient	Age (years)	Gender	Depressed					Euthymic					
			HRSD	Medication dose(mg)				HRSD	Medication dose(mg)				
1	61	F	11	TZN	75			4	MIA	20			
2	25	F						3	Free				
3	62	F						0	Free				
4	76	F	19	Free									
5	46	F	22	ZP	200	CBZ	800	6	LP	50	CBZ	800	Li 1400
6	41	F						3	LP	50	HPD	10	
7	30	F	14	Li	1000	DZP	2	8	Li	1000	DZP	2	
8	52	F	11	AMT				4	Li	600			
9	36	F						3	LP	30	Li	800	IMP 150
10	41	F	30	Li	600	CLM	100	2	Li	1000			
11	48	F	18	Li	1000			3	Li	1000	VPA	1200	
12	35	F	29	Free				5	HPD	2.3			
13	61	F	25	AMT	75	DZP	2	0	CLM	75			
14	47	M						0	Li	800	CBZ	600	
15	38	M	16	LP		AMT	50	8	Li	800			
16	43	M						3	ZP	100	Li	600	
17	43	M	27	AMT	75								
18	41	M						4	TZN	75			
Mean	45.8		20.1					3.5					
SD	12.6		6.9					2.4					

Major depression

Patient	Age (years)	Gender	Depressed					Euthymic					
			HRSD					HRSD					
1	50	F	15	THZ	75	SPD	150						
				AMT	75	CLX	6						
2	43	F	19	HPD	2.3								
3	60	F	23	DZP	15			1	AMT	150	DZP	15	
4	64	F	31	AMT	75			4	AMT	150			
5	42	F	16	DZP	6								
6	19	F	30	AMT	75								
7	56	F	33	AMT	75	CLX	6	2	AMT	125	CLX	6	
8	21	F	11	CLM	100	DZP	6						
9	51	F	14	Free									
10	65	F	18	AMT	150								
11	63	F						3	AMT	150			
12	61	F	20	DZP	6			5	AMT	150	DZP	6	
13	38	F		6	ALP	1.2							
14	56	M						5	CLM	75	CLX	6	
15	57	M	11	CLM	75								
16	52	M	27	AMT	75	CLX	6						
17	46	M	16	AMT	125								
18	49	M	14	CLM	30	DZP	6	5	CLM	30	DZP	6	
19	66	M	21	ALP	1.2			5	AMT	75	ALP	1.2	
20	54	M	25	AMT	150	CLX	6	9	AMT	150	CLX	6	
21	35	M	15	CLM	175			5	TZN	150			
22	39	M	18	AMT	75			5	AMT	150			
Mean	49.4		19.8					4.5					
SD	13.1		6.4					2					

of the patients with major depression were examined in the depressive state, and 12 in the euthymic state. They were diagnosed according to DSM-III-R after two interview sessions with senior psychiatrists for 1 h each. Their symptoms were scored using the Hamilton Rating Scale for Depression (HRSD; Hamilton 1960) on the day of the MRS examination. They were medicated with various psychotropic drugs as shown in Table 1. There were no differences in educational levels between the subject groups. Patients with a past history of substance dependence, neurological disease, or head trauma were excluded from the study. Brain magnetic resonance imaging (MRI) and computed tomography (CT) were performed in all patients and no diagnosable lesion was noted. The data for the peak area ratios in the patients with bipolar disorder in the euthymic state have already been reported in preliminary form (Kato et al. 1996).

Twenty healthy right-handed volunteers (6 men and 14 women; age 43.7 ± 9.5 years) were recruited from among the hospital staff. They were screened with a questionnaire and an interview, and those with a current or past history of mental disorders, neurological diseases, head trauma, major medical diseases, or drug abuse, or a family history of mental disorders in a first-degree relative, were excluded from the study. No diagnosable lesion was noted at brain MRI in these subjects. Written informed consent was obtained from all subjects.

^{1}H-MRS was performed with a 1.5-T whole-body MR system (SIGNA, GE Medical Systems, Milwaukee, Wis.) and a quadrature proton head coil. The volume of interest (VOI) of $3 \times 3 \times 3$ cm was selected in the left subcortical region including the caudate head, putamen, internal capsule, thalamus, and insular cortex, guided by axial T1-weighted MR imaging (Fig. 1). Stimulated echo method (STEAM) pulse sequence was applied with three chemical shift selective saturation (CHESS) pulses for water suppression (Frahm et al. 1989 a). The water proton signal gave half-peak height line width of less than 6 Hz after shimming. All spectra were obtained with repetition time (TR) of 2 s, echo time (TE) of 135 ms, 1024 data points, sweep width of 1 KHz, and 400 acquisitions.

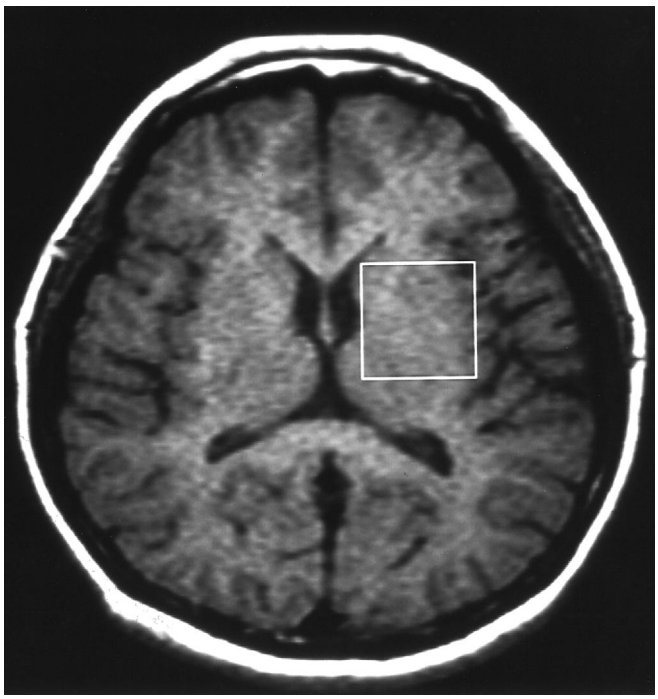

Fig. 1 T1-weighted proton magnetic resonance image in a patient with bipolar depression. The *square* indicates the volume of interest (VOI), a 3- × 3- × 3-cm voxel in the left basal ganglia

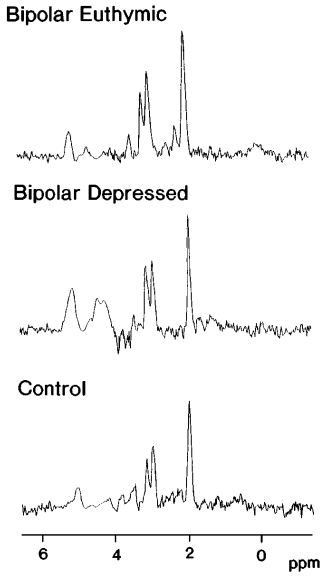

Fig. 2 Proton magnetic resonance spectra (^{1}H-MRS) from the basal ganglia of a patient with bipolar disorder in the depressive and euthymic states, and from a normal control subject. The following three peaks were evaluated: N-acetyl-l-aspartate [2.02 parts per million (ppm)], creatine and phosphocreatine (3.0 ppm), and choline-containing compounds (3.2 ppm)

The obtained data were rearranged randomly and processed by an operator who was not informed of the profile of any subject. The spectra were processed using OMEGA CSI software (GE Medical Systems) on a SPARC work station (SUN Microsystems, Palo Alto, Calif.). High-band pass filter for further water suppression (Marion et al. 1989), 1-Hz line broadening, Fourier transformation, and manual first-order phase correction were applied.

The following three peaks were evaluated: N-acetyl-l-aspartate [NAA, 2.02 parts per million (ppm)], creatine plus phosphocreatine (Cr, 3.0 ppm), and choline-containing compounds (Cho, 3.2 ppm; Fig. 2). Peak areas were calculated with personal computer using our custom-designed program for automatic curve fitting using the SIMPLEX method. Metabolite levels were evaluated as the peak ratios of Cho/Cr and Cho/NAA, as well as the absolute metabolite concentrations. Absolute concentration determination was performed according to the method by Michaelis et al. (1993). With this method the metabolite signals in the brain are compared with those from a phantom solution containing chemicals at concentrations similar to those in the brain, and effect of coil loading is corrected using the value of transmission power as follows: Conc(brainA) = Area (brainA)/Area (phanA)*Conc (phanA)*f(T2)/ρ brain where, Conc (brainA) = the concentration of metabolite A in the brain of the subject, Conc (phanA) = the concentration of metabolite A in the phantom solution, Area (brainA) = MRS peak area of metabolite A in the brain of the subject; and Area (phanA) = MRS peak area of metabolite A in the phantom solution under the same coil loading.

The phantom solution consisted of 12 mM of NAA, 4.1 mM of creatine and phosphocreatine, 1.4 mM of choline titrated with 2 mM NaOH to pH of 7.05. This standard solution was examined by ^{1}H-MRS at 15 different coil loadings. The area (phanA) was calculated from the regression line between the metabolite peak areas and the transmit attenuation values: f(T2)(T2 effect correction) = exp(–135[ms]/T2 in vivo [ms])/exp (–135[ms]/T2 in vitro [ms]).

T2 in vivo was assumed to be 360 ms, 220 ms, and 370 ms for Cho, Cr, and NAA, respectively, according to a previous report (Frahm et al. 1989 b). The T2 in vitro from the phantom solution in this study was experimentally measured and calculated to be 2067 ms, 1135 ms, and 1139 ms for Cho, Cr, and NAA, respectively. The water fraction of the human brain, ρ brain, was assumed to be 1.04 (Takagi et al. 1981).

The intra-rater coefficient of variation of the data processing was less than 10% for each of these three peak ratios. Six normal subjects were examined again on another occasion, and the inter-assay covariance was less than 20% for each of these three peaks.

For statistical analysis, Student's *t*-test, two-way analysis of covariance (ANCOVA), one-way analysis of variance (ANOVA)

with multiple comparison by Student-Newman-Keuls procedure, and Pearson's coefficient of correlation were used.

Results

Two-way ANCOVA of data for all subjects, with factors of state [major depression (depressed), major depression (euthymic), bipolar disorder (depressed), bipolar disorder (euthymic), and normal control] and gender, covariate for age, disclosed a significant effect of diagnosis on the Cho concentration ($df = 4$, $F = 3.17$, $p < 0.05$) and a significant effect of gender on the NAA concentration ($df = 1$, $F = 4.55$, $p < 0.05$). No other significant effect was found. When the peak ratios were similarly examined, significant effect of state was found in Cho/NAA ($df = 4$, $F = 4.58$, $p < 0.05$) and a similar tendency was found for Cho/Cr ($df = 4$, $F = 2.29$, $p < 0.1$).

One-way ANOVA in the five groups revealed that the Cho concentration and the Cho/NAA peak ratio of the patients with bipolar disorder in the depressive state were significantly higher than those in the patients with major depression and in the normal controls. No significant effects of state on the Cr and NAA concentrations were found (Fig. 3; Table 2).

Our hypothesis that elevation of the Cho peak is related to depressive state was examined by Student's *t*-test: The Cho concentration in the depressive bipolar patients was significantly higher than that in the normal controls ($t = 2.19$, $p < 0.05$). The Cho/Cr peak ratio in the bipolar patients in the depressed and euthymic states was significantly higher than the normal control value (depressed: $t = 1.92$, $p < 0.05$; euthymic: $t = 1.92$, $p < 0.05$), and the patients with major depression in the depressive state showed a similar tendency for the Cho/Cr peak ratio to be higher than that in the normal controls ($t = 1.55$, $p < 0.1$). The Cho/NAA peak ratio of the depressed and euthymic bipolar patients and the patients with major depression in the depressed state was significantly higher than that in

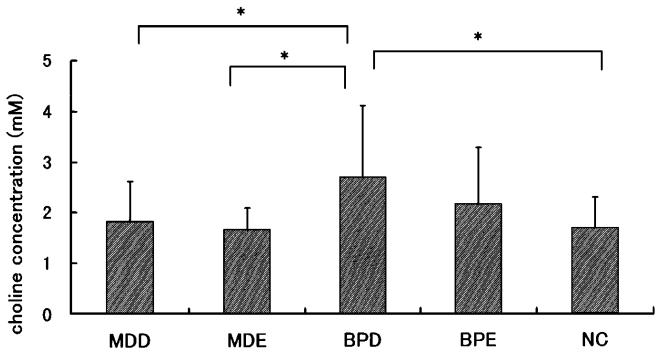

Fig. 3 Graph shows the average concentration of choline-containing compounds in each group of the subjects. The *error bar* indicates one standard deviation. *MDD* Patients with major depression in the depressive state; *MDE* patients with major depression in the euthymic state; *BPD* patients with bipolar disorder in the depressive state; *BPE* patients with bipolar disorder in the euthymic state; *NC* normal controls. ($p < 0.05$)

Table 2 State effects on metabolites. CHO choline-containing compounds

	n	Age (years)	Education year	Concentration		Peak Ratio			
				Cho (mM)	Cr (mM)	NAA (mM)	Cho/Cr	Cho/NAA	NAA/Cr
Major Depression Depressed (group 1)	19	M = 8 F = 11	48.94 ± 13.45	11.364 ± 3.35	1.824 ± 0.79	8.154 ± 3.44	15.804 ± 4.82	0.6874 ± 0.256	0.4084 ± 0.136[c]	1.7334 ± 0.600
Major Depression Euthymic (group 2)	12	M = 6 M = 6	53.414 ± 10.79	10.914 ± 4.29	1.664 ± 0.42	8.734 ± 2.68	16.254 ± 4.89	0.5684 ± 0.181	0.3704 ± 0.074	1.5724 ± 0.501
Bipolar Disorder Depressed (group 3)	11	M = 2 F = 9	48.274 ± 13.44	11.904 ± 1.13	2.704 ± 1.46[a]	9.364 ± 2.17	17.144 ± 3.78	0.8754 ± 0.511[c]	0.5614 ± 0.287[b] [e]	1.5364 ± 0.347
Bipolar Disorder Euthymic (group 4)	16	M = 4 F = 12	44.374 ± 10.91	11.754 ± 1.77	2.164 ± 1.13	8.254 ± 2.64	16.794 ± 4.03	0.7754 ± 0.387[d]	0.4334 ± 0.161[f]	1.8124 ± 0.679
Normal Control (group 5)	20	M = 6 F = 14	43.754 ± 9.54	14.004 ± 5.27	1.684 ± 0.61	9.704 ± 3.25	18.484 ± 4.07	0.5544 ± 0.278	0.3204 ± 0.098	1.7094 ± 0.647

[a] Compared with groups 1, 2, 5 with one-way ANOVA ($F = 2.88$, $p < 0.05$)
[b] Compared with groups 1, 2, 4, 5 with one-way ANOVA ($F = 4.51$, $p < 0.05$)
[c] Compared with group 5 with Student's *t*-test ($t = 1.92$, $p < 0.05$)
[d] Compared with group 5 with Student's *t*-test ($t = 1.92$, $p < 0.05$)
[e] Compared with group 5 with Student's *t*-test ($t = 2.72$, $p < 0.01$)
[f] Compared with group 5 with Student's *t*-test ($t = 2.47$, $p < 0.05$)

the normal controls (bipolar patients in the depressive state: $t = 2.72$, $p < 0.05$; bipolar patients in the euthymic state: $t = 2.47$, $p < 0.05$; major depression in the depressive state: $t = 2.30$, $p < 0.05$).

When paired *t*-test was applied to the 9 bipolar patients and 9 patients with major depression who were examined in both the depressive and euthymic states, no significant state-dependent difference was found in metabolite concentrations and peak ratios.

To clarify the effect of gender on the NAA concentration found by two-way ANCOVA, we applied an exploratory *t*-test. The absolute concentration of NAA in men with major depression in the depressive state was significantly higher than that in the depressive women ($t = 2.44$, $p < 0.05$).

No significant effect of age, duration of illness, HRSD score, or educational level were found.

No significant effect of the subtype of bipolar disorder (bipolar disorder and bipolar-II disorder) was found using Student's *t*-test. The effect of medications was also examined with Student's *t*-test. Patients with bipolar disorder treated with antipsychotics ($n = 20$) had significantly higher Cr concentration than those treated without these drugs ($n = 7$). Bipolar patients treated with anticonvulsants ($n = 23$) had significantly higher NAA concentration than those treated without these drugs ($n = 4$). Patients with major depression treated with benzodiazepines had significantly lower Cr concentration than those treated without these drugs. No significant effect of medications was found for the Cho concentration, Cho/Cr, or Cho/NAA.

Discussion

In this study the Cho concentration in the patients with bipolar disorder in the depressive state was increased compared with that in the normal controls. Charles et al. (1993) and Renshaw et al.(1994) noted significant elevation of the Cho/Cr peak ratio in the subcortical region including the basal ganglia like that observed in our study in drug-free patients with major depression. In this study the peak ratios of Cho/Cr and Cho/NAA were significantly elevated in both major depression (only in the depressive state) and bipolar disorder (both in the depressive and euthymic state), whereas the Cho concentration was not significantly increased in major depression. We hypothesize that the observed increases of the Cho/Cr and Cho/NAA peak ratios in the patients with major depression were due to synergism of increase of Cho and decrease of Cr and NAA, although this is speculative because significant alteration of absolute concentration was not found in these patients. On the other hand, the absolute concentration of Cho was significantly elevated in the depressive patients with bipolar disorder. However, it is still not clear from our results whether increase of Cho concentration in bipolar disorder is state dependent or trait dependent.

The Cho peak detected by ^{1}H-MRS consists of signals from phosphocholine, glycerophosphocholine (GPC), and free choline (Miller et al. 1996). Most of these metabolites are related to membrane phospholipid metabolism. Christensen et al. (1994) first reported an increase of the phosphodiester (PDE) peak in the basal ganglia of patients with major depression observed using ^{31}P-MRS. Because GPC is a component of PDE peak, they speculated that increase of GPC may have contributed to this increase. If so, membrane catabolism may be accelerated in the basal ganglia of patients with affective disorders. However, this finding of increased PDE peak was not confirmed in their subsequent study in drug-free patients with major depression (Moore 1996).

One of the limitations of this study was the heterogeneity of the VOI we examined. The VOI contains the basal ganglia, internal capsule, thalamus, cerebrospinal fluid, and other nearby structures. The inter-individual variability of the constitution of these structures in the VOI might have caused the relatively large variance of the metabolite peak ratios in our results, as it is known that the concentrations of these metabolites differ in the gray matter and in the white matter (Christiansen et al. 1993). Thus, we cannot conclude that the changes of the peak areas observed are solely due to alteration of metabolism in the basal ganglia. However, this does not entirely preclude comparison of our data with the results reported by Sharma et al. (1992) and by Charles et al. (1993), who examined a region similar to that we studied.

Our failure to control medication also complicates the interpretation of the data obtained; we could not discontinue the medication due to ethical reasons. Our subjects were under treatment with several drugs in various combinations. Though we conducted a preliminary analysis of the effect of medications, further investigation is needed to examine this effect.

Although this type of ^{1}H-MRS study cannot be made of the above-noted technical limitations, this is the first report indicating increase of the absolute concentration of choline-containing compounds in the subcortical region in bipolar depression.

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