Choline-Containing Compounds Detected by Proton Magnetic Resonance Spectroscopy in the Basal Ganglia in Bipolar Disorder

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Choline-containing compounds (Cho) were examined by proton magnetic resonance spectroscopy (^{1}H-MRS) in the left subcortical region, including basal ganglia, in 19 euthymic patients with bipolar disorder and 19 age-matched normal controls. Ten of the patients were treated with lithium; the remaining 9 were not treated with lithium for at least 30 d. The Cho to creatine + phosphocreatine (Cr) peak ratio in the bipolar patients (0.75 ± 0.38 [mean ± SD]) was higher than that in the normal controls (0.52 ± 0.26, $P < 0.05$). There was no significant difference in the Cho:Cr peak ratio between patients treated with lithium (0.63 ± 0.36) and without lithium (0.89 ± 0.35). These results do not support the hypothesis that lithium increases the brain choline-containing compounds, but rather imply that membrane breakdown may occur in the basal ganglia of patients with bipolar disorder.

Key Words: bipolar affective disorder, manic-depressive illness, lithium, brain imaging

INTRODUCTION

Since the report that lithium irreversibly inhibits the transport of choline in red blood cells (RBC) (Lee and others 1974), this effect has attracted considerable attention because it might be related to clinical efficacy. In patients treated with lithium, a 10-fold increase of RBC choline has been reported (Jope and others 1978). This accumulation of choline in RBCs is thought to be caused by the inhibition of elimination of choline made by breakdown of membrane phospholipids (Domino 1995). Although this effect does not directly relate to clinical efficacy for patients with bipolar disorder, it may be due to the difference between choline transport in the RBC and brain (Domino 1995). Because this dramatic effect of lithium on choline transport is not observed in animals, but is specific to humans (Krell and Goldberg 1973), it is difficult to study this effect in the brain.

^{1}H-MRS can noninvasively detect Cho in the human brain (Miller 1991) in vivo. Although the Cho peak detected by ^{1}H-MRS includes signals not only from free choline but also from other soluble choline-containing compounds such as glycerophosphocholine and phosphocholine (Domino 1995), it is worthwhile examining whether or not this peak increases in patients treated with lithium.

Sharma and others (1992) 1st applied ^{1}H-MRS to patients with bipolar disorder. They reported that the Cho:Cr peak ratios in the basal ganglia of 4 bipolar disordered patients treated with lithium were somewhat higher than those in

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Table 1

Characteristics of the subjects

Subjects	Age[a]	Sex	Education[a]	Age at onset[a]	Subtype
Controls	40.3 ± 6.3	F 14, M 5	13.7 ± 3.5	–	–
				–	–
Bipolar disorder					
With lithium	39.7 ± 6.8	F 7, M 3	11.9 ± 1.9	26.9 ± 8.2	BP I 7, BP II 3
Without lithium	43.8 ± 11.2	F 7, M 2	11.4 ± 1.4	37.0 ± 10.5	BP I 3, BP II 6

[a]mean ± SD.
(–) represents data unavailable.

normal controls, while there was no difference in the values obtained for the occipital cortex. No difference in the Cho:Cr peak ratio in the cerebral cortex of bipolar patients treated with lithium was confirmed by other investigators (Stoll and others 1992; Bruhn and others 1993). Recently, Lafer and others (1994) reported that the Cho:Cr peak ratio was increased in the basal ganglia in bipolar patients treated with lithium. It has also been reported that lithium levels in the human brain after chronic lithium treatment were higher in the basal ganglia than those in the cerebral cortex (Spirtes 1976), further suggesting that the effect of lithium on choline metabolism may be limited to the basal ganglia. This possible effect of lithium on basal ganglia choline metabolism is of particular interest because the basal ganglia are implicated in the pathophysiology of affective disorders (Guze and Gitlin 1994). It is not yet clear, however, whether an increase in the Cho peak relates to lithium administration or to the pathophysiology of bipolar disorder because a similar increase is also reported in major depression (Charles and others 1994; Renshaw and others 1994).

The purpose of this study is to examine the effect of lithium on brain choline resonance detected by ^{1}H-MRS in patients with bipolar disorder treated with and without lithium.

Subjects

Clinical evaluation

The subjects were 19 right-handed inpatients (14 females and 5 males; mean age ± SD, 41.6 ± 9.4 y) who had been diagnosed as having bipolar I disorder (BP I, n = 10) or bipolar II disorder (BP II, n = 9) according to the DSM-III-R criteria (American Psychiatric Association 1987). Diagnoses were made by senior psychiatrists through 2 interview sessions of 1 h each. Psychiatric state was evaluated by Petterson Mania Rating Scale and Hamilton Rating Scale for Depression. The patients were examined in the remission state, having had no clinical signs or symptoms of mania or depression for at least 2 weeks before the study. No patient had a past history of drug dependence, neurological disease, or head trauma. All patients were examined by MRI, and no major structural abnormalities in the brain were noted.

Nineteen healthy right-handed volunteers whose ages and sexes were matched with the patients (40.3 ± 6.3 y, 14 females and 5 males) were selected from hospital staff. They were screened for past history of mental disorders, neurological disease, head trauma or major medical disease, family history of mental disorders in 1st-degree relatives, and current use of any drugs by a questionnaire and an interview. Subjects with such history were excluded from the study. No major structural abnormality in the brain was noted by MRI in any normal controls.

All subjects gave written informed consent prior to participation in the study.

Drug administration

The patients were divided into 2 groups: 1 group was treated with lithium, and the other was treated without lithium (Table 1).

The former group (n = 10) was treated with lithium carbonate, 840 ± 233 (mean ± SD) mg/d, dose range of 600 to 1400 mg/d. They were treated with lithium for more than 40 d and were in a steady state. The dose of lithium was decided by the attending physicians, with dosage always sufficient to maintain a serum lithium concentration of 0.4 mM, the minimum recommended concentration in Japan. Patients were medicated with various psychotropic drugs other than lithium including antipsychotics (zotepin 50 to 200 mg/d [n = 4], haloperidol 10 mg/d [n = 1], and levomepromazine 30 mg/d [n = 1]), antidepressant (imipramine 150 mg/d [n = 1]), and anxiolytic medication (cloxazoram

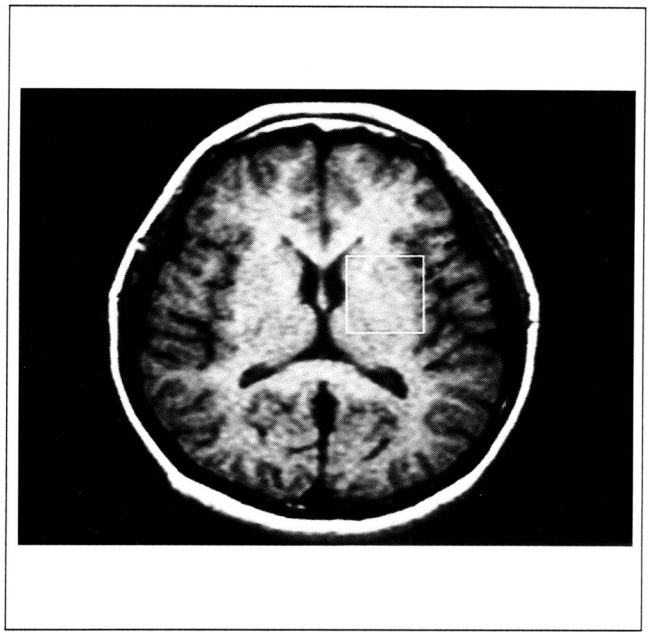

Figure 1. T1-weighted proton magnetic resonance image in a patient with bipolar disorder. The square indicates the VOI, a 3 × 3 × 3 cm voxel in the left basal ganglia.

2 mg/d [n = 1]). Although 1 of these patients had a history of thyroid dysfunction treated with triiodothyronine 0.5 μg/d, normal thyroid function was observed when ^{1}H-MRS was performed.

The other group (n = 9) was not treated with lithium for at least 30 d. Three of these subjects have never been treated with lithium. The other 6 patients were free of lithium for 30 to 120 d (76.5 ± 36.0 d). In 2 of the 6, a lack of response to lithium treatment prompted the switch to other mood stabilizers. In 2 others, lithium had been stopped because of side effects. The remaining 2 subjects in this group discontinued the lithium therapy of their own accord. The 9 nonlithium-treated subjects were treated with various psychotropic drugs as follows: antidepressants (mianserin 20 mg/d [n = 1] and trazodone 75 mg/d [n = 1]); antipsychotics (haloperidol 1.5 to 2.25 mg/d [n = 2], sulpiride 600 mg/d [n = 1], and levomepromazine 50 mg/d [n = 1]); carbamazepine (800 mg/d [n = 1]); clonazepam (2 mg/d [n = 1]); and anxiolytics (diazepam 6 mg/d [n = 1]). One patient was given triiodothyronine (0.25 μg/d) as a mood stabilizer. Two patients had a history of thyroid dysfunction, but their thyroid function was normal at the time of the study and did not require hormone treatment.

There were no significant differences in age, sex, and education between these 2 groups. The latter group included more patients with a BP II diagnosis (n = 6) than the former group (n = 3). The age of onset was significantly higher in the nonlithium-treated group (see Table 1).

METHODS

^{1}H-MRS was performed with a 1.5-tesla SIGNA MR system and a quadrature proton head coil (GE Medical Systems, Milwaukee, WI). T1-weighted spin-echo MRI was performed, and the volume of interest (VOI) was determined with the 3 × 3 × 3 cm voxel centered on the left basal ganglia, including the head of the caudate nucleus and the lenticular nucleus (Figure 1). After the location of the VOI was verified with localized MRI, the magnetic field in the VOI was optimized by water signal enough to establish the line width at less than 6 Hz. After the water suppression pulse was optimized, ^{1}H-MR spectra were obtained by stimulated echo method (STEAM) pulse sequence (Frahm and others 1989) with chemical shift selective saturation (CHESS) pulse, with the repetition time (TR) of 2 sec, echo time (TE) of 135 msec, 1024 data points, and spectral width of 1000 Hz. Four hundred acquisitions were averaged.

The data obtained were numbered, randomly ordered, and processed by a single operator who was blind to the diagnosis. Data processing was conducted at a SPARC work station (SUN Microsystems, USA) with OMEGA software (GE Medical Systems, USA). Low-cut filter (Marion and others 1989), 1-Hz line-broadening, Fourier transformation, and manual 1st-order phase correction were applied. When water suppression was incomplete, additional baseline correction with polynomial interpolation was applied. Following the lead of Miller (1991) we assigned the following 3 peaks: N-acetyl-L-aspartate (NAA, 2.02 parts per million [ppm]); creatine + phosphocreatine (Cr, 3.0 ppm); and choline-containing compounds (Cho, 3.2 ppm) (Figure 2). Peak areas

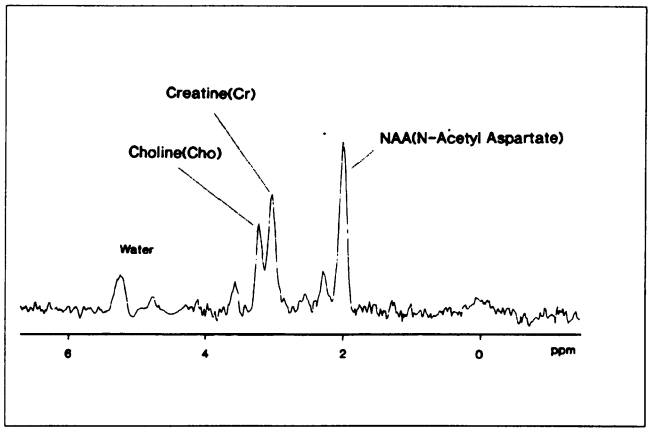

Figure 2. ^{1}H-MRS from the basal ganglia of a patient with bipolar disorder. NAA: N-acetyl-L-aspartate, Cr: creatine + phosphocreatine, Cho: choline-containing compounds.

were calculated by automatic curve fitting with SIMPLEX method using software programmed in our laboratory for use with an IBM personal computer. Peak areas were expressed as peak area ratios.

The interassay coefficients of variation (CVs) of the 3 peak ratios (Cho:Cr, NAA:Cr, and Cho:NAA) in 6 subjects examined at 2 independent sessions were found to be within 20%.

For statistical analysis, Student's t test, 1-way analysis of variance (ANOVA) with multiple comparison by Student-Newman-Keuls procedure, and Pearson's coefficient of correlation were used.

RESULTS

Effect of lithium

The Cho:Cr peak ratio in the 19 patients with bipolar disorder was significantly higher than that in the normal controls ($t = 2.1$, df = 36, $P < 0.05$) (Table 2). The Cho:NAA peak ratio in the bipolar patients was also slightly higher than that in the normal controls ($t = 1.9$, df = 36, $P = 0.057$), although the difference was not statistically significant. Both of these differences were significant if patients with a history of thyroid disease were excluded (Cho:Cr, $P < 0.05$, df = 33, $t = 2.2$; Cho:NAA, $P < 0.05$, df = 33, $t = 2.1$). There was no significant difference in the NAA:Cr peak ratio between patients and normal controls.

No significant differences in these 3 peak area ratios were found between patients treated with lithium and patients treated without lithium (see Table 2). The Cho:Cr peak ratio was rather higher in patients treated without lithium compared with those treated with lithium, although the difference was not significant. Patients treated without lithium had significantly higher Cho:Cr ($t = 2.9$, df = 26, $P < 0.01$, Student's t test) and Cho:NAA ($t = 2.6$, $P < 0.05$) peak ratios than normal controls.

Background factors

Other drugs and diagnostic subtypes were examined to determine the extent of their role as confounding factors. When all patients were divided into pairs of groups treated with and without antidepressants and antipsychotics, no significant effect of antipsychotic medication on the 3 peak area ratios was found. Significant differences, however, were found in the Cho:Cr and Cho:NAA peak ratios between the patients treated with antidepressants (Cho:Cr, 1.23 ± 0.26; Cho:NAA, 0.62 ± 0.008) and without antidepressants (Cho:Cr, 0.66 ± 0.34, $P < 0.05$, df = 17, $t = 3.2$; Cho:NAA, 0.37 ± 0.14, $P < 0.05$, $t = 2.2$).

A 2-way ANOVA with covariates of diagnostic groups (BP I, BP II, and normal controls) and lithium treatment was applied to determine the confounding effect of diagnostic subtypes. No significant effect of lithium was found in the 3 peak ratios. A significant effect of diagnostic groups was found for the Cho:Cr peak ratio ($F = 5.25$, $P < 0.02$). The Cho:NAA peak ratio also tended to be affected by diagnostic groups ($F = 3.08$, $P = 0.05$). When multiple comparison with Student-Newman-Keuls procedure was applied, the Cho:Cr peak ratio in the BP II patients (0.92 ± 0.42) was higher than that in the BP I patients (0.60 ± 0.26, $P < 0.05$) and the normal controls (0.52 ± 0.26, $P < 0.05$). These differences remained significant when patients with thyroid disease were excluded ($P < 0.05$, $P < 0.05$, respectively).

To examine which factor, antidepressant medication or diagnostic subtype, contributed to the elevated Cho:Cr and Cho:NAA peak ratios, 2-way ANOVA by these 2 factors with a covariate of age was applied. Significant effect of antidepressant was found both in the Cho:Cr ($F = 7.5$, $P < 0.05$) and the Cho:NAA ($F = 6.1$, $P < 0.05$) peak ratios, while no significant effect of diagnostic subtype was found in either of these peak ratios (Cho:Cr, $F = 1.9$, $P > 0.10$; Cho:NAA, $F = 0.1$, $P > 0.10$).

Even if patients treated with antidepressants were excluded from the patients without lithium, the Cho:Cr ratio was significantly higher (0.84 ± 0.38, $t = 2.2$, df = 24, $P < 0.05$) compared with normal controls and higher, though not significantly so, than those treated with lithium (0.53 ± 0.20, $t = 1.9$, df = 14, $P < 0.10$).

No significant difference was found for any of these peak ratios in comparisons between females and males, between

Table 2

Results in proton MRS

Subjects	Cho:Cr[a]	NAA:Cr[a]	Cho:NAA[a]
Controls (N = 19)	0.52 ± 0.26	1.59 ± 0.47	0.32 ± 0.09
Bipolar disorder (N = 19)	0.75[b] ± 0.38	1.83 ± 0.61	0.41 ± 0.15
With lithium (n = 10)	0.63 ± 0.36	1.68 ± 0.55	0.37 ± 0.14
Without lithium (n = 9)	0.89[b] ± 0.35	2.00 ± 0.63	0.45[b] ± 0.15

[a]mean ± SD.
[b]$P < 0.05$ to normal controls by Student's t test.

patients with a past history of psychotic symptoms (n = 12) and those without, or between rapid cyclers (n = 4) and nonrapid cyclers.

In a further examination of the effect of background factors, the correlation of these 3 peak ratios with age and age at onset in the bipolar patients was analyzed. The NAA:Cr peak ratio was significantly negatively correlated with age ($r = -0.46$, $P < 0.05$) in the patients. The other 2 peak ratios did not significantly correlate with age (Cho:Cr, $r = -0.20$; Cho:NAA, $r = 0.12$). The correlation between the NAA:Cr peak ratio and age was not found in the normal controls ($r = 0.09$, $P > 0.10$). The 3 peak ratios did not correlate with age at onset (Cho:Cr, $r = 0.03$; Cho:NAA, $r = 0.15$; NAA:Cr, $r = -0.17$).

DISCUSSION

In this study, patients treated with lithium did not have higher Cho:Cr and Cho:NAA peak ratios compared with normal controls or patients treated without lithium. On the contrary, the Cho:Cr peak ratio was significantly higher in patients treated without lithium compared with normal controls and tended to be higher than in patients treated with lithium. Because the Cho:NAA peak ratio was also higher, this elevation seems to be due to the increase of the Cho peak. This unexpected finding suggests that the Cho peak in this region is elevated in patients with bipolar disorder unrelated to lithium treatment. Whether or not lithium treatment decreases this elevated Cho peak is not clear from the present results. A preliminary report by Lafer and others (1994) has also mentioned that the Cho:Cr peak ratio in the basal ganglia was significantly higher than in normal controls and that no distinct difference exists between the peak ratios of patients treated with and without lithium.

As Stoll and others (1992) have demonstrated, we cannot conclude that lithium does not increase choline in the brain because the Cho peak observed by ^{1}H-MRS contains signals from many other choline-containing compounds. Nevertheless, because other choline-containing compounds in RBCs, such as phosphocholine and phosphatidylcholine, are also reported to be increased after lithium treatment (Pleul and Muller-Oerlinghausen 1986), it is unlikely that lithium increases the concentration of Cho in the brain.

Some investigators have reported that the Cho:Cr peak in the subcortical region, including the basal ganglia, was increased in drug-free patients with major depression (Charles and others 1994; Renshaw and others 1994). Other studies also noted abnormality in the basal ganglia in affective disorders. These include low glucose metabolism (Baxter and others 1985; Buchsbaum and others 1986), frequent association of poststroke depression with basal ganglia lesions (Starkstein and others 1987), and reduced volume of caudate nuclei in major depression (Krishnan and others 1992). Basal ganglia, therefore, are implicated in the pathophysiology of bipolar disorder (Guze and Gitlin 1994). The present results, together with the findings in ^{1}H-MRS studies by other investigators (Sharma and others 1992; Charles and others 1994; Lafer and others 1994; Renshaw and others 1994) also indicate that this region has a metabolic abnormality in affective disorders.

It is unclear which choline-containing compounds contribute to the increase of the Cho peak. The Cho peak consists of signals from phosphocholine (PC), glycerophosphocholine (GPC), phosphatidylcholine, choline, acetylcholine, and sphingomyelin, although the exact extent of contribution from each of them is not yet well known (Miller 1991; Domino 1995). Increase of the Cho peak observed in acute plaques of multiple sclerosis (Arnold and others 1990; Koopmans and others 1993) is thought to reflect demyelination. The Cho peak also increases in other neuronal degenerative diseases such as Alzheimer's disease (Meyerhoff and others 1994) and Huntington's disease (Jenkins and others 1993), but is accompanied by a decrease of NAA. Recently, Christensen and others (1994) speculated that the increase of the Cho peak in the basal ganglia in patients with major depression may be due to the increase of GPC, a membrane breakdown product, because the phosphodiester peak observed by ^{31}P-MRS, which contains GPC, was also increased in the basal ganglia in patients similarly diagnosed. This speculation that membrane breakdown occurs in the basal ganglia of patients with affective disorders coincides with several lines of evidence implicating alteration of membrane phospholipid metabolism in bipolar disorder (Kato and others 1991, 1992, 1993, 1994; Deicken and others 1994, 1995).

Although a significant effect of antidepressants was found in this study, the number of patients treated with antidepressants (n = 3) was too small to conclude that they affect the brain Cho peak. In addition, Charles and others (1994) have reported the change of the Cho peak to be opposite to our results, that is, to decrease after the antidepressant treatment.

The significant negative correlation between the NAA:Cr peak ratio and age is also an intriguing finding. NAA is abundant in neurons, whereas most glial cells do not contain this metabolite. NAA has been thought, therefore, to be a marker of viable neurons (Urenjak and others 1993). NAA decreases in neurodegenerative disorders (Jenkins and others 1993; Meyerhoff and others 1994). If the observed negative correlation of the NAA:Cr peak area ratio with age was due to a decrease of NAA, an age-dependent progression of neuronal loss in the basal ganglia in bipolar disorder may be implied.

It should be noted that the results of this study must be interpreted with caution. Increase of the Cho peak might be dismissed because we did not apply absolute concentration

determination. The peak area examined was also affected by relaxation times. Because the VOI used in this study is relatively large (3 × 3 × 3 cm), it contains signals from basal ganglia, internal capsule, thalamus, CSF, and other structures nearby. We cannot say, therefore, that the observed difference of metabolites correctly reflects the metabolism of the basal ganglia. It cannot be ruled out that the observed difference of peak ratios may reflect the difference of the size of caudate nuclei because it was reported that the volume of caudate nuclei was reduced in major depression (Krishnan and others 1992). We used this voxel size, however, to establish a basis for comparison of our results with the results other studies using similar VOIs (Charles and others 1994; Sharma and others 1992).

Other factors also confounded the results. Uncontrolled medications in this study have complicated the interpretation of the data. Differences in diagnostic subtypes or age at onset between patients treated with and without lithium may have affected the results. It should be noted that half of the bipolar patients in this study had BP II disorder, for which the pathophysiology may not be the same as it is in BP I disorder. Other clinical characteristics that caused discontinuation of lithium treatment may also have affected the results. Although the best way to examine the effect of lithium on the Cho resonance in the brain is to examine ^{1}H-MRS before and after the washout of lithium treatment, this method is not ethical because discontinuation of lithium frequently causes relapse.

Further study by advanced MRS techniques, such as MR spectroscopic imaging and absolute quantification, may clarify the ambiguity of the finding of the elevated Cho:Cr peak ratio in bipolar disorder.

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