

Reduced Cortical γ -Aminobutyric Acid Levels in Depressed Patients Determined by Proton Magnetic Resonance Spectroscopy

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Background: Several lines of emerging evidence suggest that dysfunction of γ -aminobutyric acid (GABA) systems is associated with major depression. However, investigation of this hypothesis is limited by difficulty obtaining noninvasive in vivo measures of brain GABA levels. In this study we used in vivo proton magnetic resonance spectroscopy to investigate the hypothesis that abnormalities in the GABA neurotransmitter system are associated with the neurobiologic processes of depression.

Methods: The GABA levels were measured in the occipital cortex of medication-free depressed patients meeting DSM-IV criteria (n = 14) and healthy control subjects with no history of mental illness (n = 18) using a localized difference editing proton magnetic reso-

nance spectroscopy protocol. An analysis of covariance was employed to examine the effects of depression, sex, and age.

Results: The depressed patients demonstrated a highly significant (52%) reduction in occipital cortex GABA levels compared with the group of healthy subjects. While there were significant age and sex effects, there was no interaction of diagnosis with either age or sex.

Conclusion: This study provides the first evidence of abnormally low cortical GABA concentrations in the brains of depressed patients.

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DESPITE PREVALENCE rates as high as 17%,¹ significant gaps remain in our understanding of the pathophysiological processes associated with major depressive disorder. The last 3 decades of research have highlighted the role of the biogenic amines and the hypothalamic-pituitary-adrenal axis in the neurobiological processes of this disorder. However, emerging evidence suggests the γ -aminobutyric acid (GABA) system may also contribute to the pathophysiological characteristics and pharmacological treatment of depression.²

Several lines of preclinical and clinical investigation provide this evidence. Rodent studies describe decreased GABA concentrations and receptor function in several brain regions in response to both acute and chronic stress.³⁻⁵ In addition, the administration of GABA agonists prevents and reverses rodent behavioral models of depression,⁶ whereas administration of GABA antagonists produces behaviors that mimic these models.⁷ In humans, supportive evidence of a GABA-

ergic contribution to the pathophysiological processes and the treatment of mood disorders comes from clinical trials demonstrating potent antidepressant and mood-stabilizing properties of several compounds with GABA-mimetic activity.⁸⁻¹² Reports of abnormal findings in plasma and cerebrospinal fluid (CSF) GABA levels in depressed patients compared with healthy control subjects further suggest the disorder is associated with a GABAergic dysfunction. Most of these studies demonstrated decreased GABA levels in the depressed patients.¹³⁻¹⁷ However, interpretation of these studies is limited by the existence of a CSF GABA concentration gradient¹⁸ and the inability to localize the origin of the measured GABA.

Recently developed proton magnetic resonance spectroscopy techniques enable the direct measurement of brain GABA levels in vivo through a noninvasive procedure.^{19,20} This technique was previously used to show altered occipital cortex GABA levels in association with seizure disorder²¹ and alcoholism.²² The

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SUBJECTS, MATERIALS, AND METHODS

SUBJECTS

Fourteen depressed patients (8 men, 6 women) were studied after obtaining written informed consent using forms and procedures approved by the Yale University Human Investigations Committee, New Haven, Conn. Depressed patients were recruited through local advertisements and referrals from community psychiatrists. All depressed patients met DSM-IV²⁵ criteria for major depressive disorder on the basis of a structured clinical diagnostic interview.²⁶ A summary of the subjects' clinical histories is provided in the **Table**. None of the subjects had current substance abuse disorders or histories of substance dependence disorders. All subjects reported minimal alcohol intake over the last several weeks prior to the magnetic resonance spectroscopy session. The mean age \pm SD of the depressed patients was 42.9 \pm 9.2 years (men, 47.6 \pm 5.5 years; women, 36.5 \pm 9.7 years). Patients were at least moderately depressed as reflected by the 25-item Hamilton Depression Rating Scale scores (mean \pm SD, 34.0 \pm 7.0; score range, 24-47). Subjects completed a minimum 2-week medication washout prior to spectroscopy. One patient required a low dose of lorazepam (0.5 mg, 3 times daily) for clinical management in the 2 weeks prior to spectroscopy. Another patient required thioridazine hydrochloride (50 mg) on 5 occasions for severe anxiety during the 2-week washout. One control subject and 1 depressed

patient were postmenopausal, and both women were undergoing hormone replacement therapy at the time of the study.

Eighteen healthy control subjects (11 men; 7 women) with no history of major depression or other DSM-IV diagnoses were studied. The control subjects were recruited through local advertisements and from the Yale research staff. The mean \pm SD age of the control subjects was 38.4 \pm 10.2 years, (men, 41.1 \pm 8.6 years; women, 34.1 \pm 11.7 years). Minimum alcohol intake was reported by all of the control subjects participating in this study.

MAGNETIC RESONANCE SPECTROSCOPY PROTOCOL

The GABA measurements were obtained according to the method described by Rothman et al.²⁰ Briefly, studies were performed at the Yale University School of Medicine with a 2.1T Oxford Magnet (Oxford Magnetic Technology, Oxford, England) with a 1-m bore, equipped with a Bruker Biospec Avance 1 spectrometer (Bruker Instruments, Billerica, Mass). Subjects lay supine with the occipital cortex apposed to an 8-cm radiofrequency surface coil tuned to the proton nuclear magnetic resonance frequency of 89.43 MHz. Prior to the magnetic resonance spectroscopy measurement, gradient echo-scout images of the subject's brain were obtained. A 1.5 \times 3 \times 3-cm volume of interest centered on the midline of the occipital cortex, 2 cm deep from the dura, was chosen for spectroscopic measurement. An automated first- and second-order shimming routine

Demographic Data and Patient Clinical History*

Characteristic	Patient No.						
	1	2	3	4	5	6	7
Sex/age, y	M/51	M/50	M/50	M/48	M/47	M/47	M/45
Additional clinical features†	...	Psychotic	Psychotic, catatonic	...	Psychotic	...	Comorbid OCD
Previous psychiatric history†	1 Previous MDE, >20 y ago	3 MDEs, alcohol abuse, complete remission, 1 y	3 MDE	Dysthymia, nondiscrete MDE	Nondiscrete MDE
Episode duration, mo	19	5	11	>60	12	3	>60
No. of suicide attempts	0	0	0	0	1	0	0
Medication history	Treatment resistant	<1 wk treatment 1 mo prior to study	Treatment resistant	Treatment resistant	Treatment resistant	Multiple treatments, no medications >1 mo	Treatment resistant

*OCD indicates obsessive-compulsive disorder; BPD, borderline personality disorder; SP, social phobia; MDE, major depressive episode; treatment resistant, a history of 3 or more antidepressant medication trials without significant improvements; TCA, tricyclic antidepressant medication; and ellipses, none. †Defined by DSM-IV criteria.

objective of our current study was to determine if GABA levels are abnormal in the brains of depressed patients compared with healthy control subjects. The occipital cortex was chosen in this study based on technical limitations and previous findings of reduced occipital cortex GABA levels in alcohol-dependent²² and seizure disorder patients,²¹ 2 conditions that are frequently associated with elevated rates of depression.^{23,24}

RESULTS

Medication-free depressed patients (n = 14) had markedly lower occipital cortex GABA_(total) concentrations (mean \pm SD, 0.71 \pm 0.27 mmol/kg) than healthy control subjects (n = 18) (mean \pm SD, 1.48 \pm 0.39 mmol/kg), as illustrated in 2 representative spectra in **Figure 1**. The difference was significant by 1-way ANCOVA covarying

was used to optimize B_0 homogeneity in the volume of interest.^{27,28}

Homonuclear editing of the 3.0 ppm (chemical shift scale; ppm) GABA C4 resonance was performed using the J-editing pulse sequence described previously.²⁰ Spectral editing detects signals from hydrogen atoms that are J-coupled to hydrogen atoms on adjacent carbon atoms in the same molecule. In this case the spin-spin J editing selected the GABA C4 triplet resonance at 3.0 ppm, which is coupled to the GABA C3 multiplet resonance at 1.9 ppm. Two subspectra of 128 scans each were subtracted to obtain a difference spectrum that isolates GABA_(total) (combined measure of GABA and the GABA-containing dipeptide homocarnosine). The localization techniques included 3-dimensional, image-selected, in vivo spectroscopy with outer volume suppression, selective excitation, and use of a surface spoiler coil. The spectral acquisition parameters were as follows: repetition time, 3.39 seconds; echo time, 68 milliseconds; sweep width, 1500 Hz; and acquisition time, 510 milliseconds. A chemical shift-selective 80-millisecond hyperbolic secant pulse followed by an inversion recovery delay and a 2-2 refocusing pulse were used for water suppression. Spectral editing of the GABA C4 resonance at 3.0 ppm was achieved by applying a delays alternating with nutations for tailored excitations (DANTE) pulse to invert selectively the 1.9 ppm C3 resonance.²⁰ The 26.5-millisecond DANTE editing pulse was applied symmetrically in time about the center of the refocusing pulse sequence. The free induction decay was zero-filled to 32 K, and a 3-Hz exponential filter was applied before Fourier

analysis. The GABA signal was integrated over a 0.30-ppm bandwidth at 3.00 ppm. The creatine signal was integrated over a 0.20-ppm bandwidth at 3.00 ppm in the GABA-inverted spectrum. The following equation was used to calculate the GABA concentration: $[GABA] = ([G^*/Cr^*] - [M/Cr^*]) (ICF) (EE) (3/2) ([Cr])$, where G^* is the integral in the edited spectrum; Cr^* , the integral of the creatine resonance; M , the contribution to the edited GABA spectrum from edited macromolecule resonances^{20,29,30}; ICF, the correction for the limited integral bandwidths determined from localized edited spectra of solutions of GABA and line-broadened creatine to match the in vivo processed line widths; EE, the correction for loss of intensity due to imperfect editing efficiency; 3:2, the creatine/GABA_(total) proton ratio; and $[Cr]$, 9 mmol/kg wet weight—the creatine concentration in the human occipital cortex.³¹

STATISTICAL ANALYSIS

Analysis of covariance (ANCOVA) was employed to determine group differences, controlling for age and sex effects in the sample populations. Similar ANCOVAs using Bonferroni adjustments were employed for post hoc group comparisons. To evaluate the covariance of age and cortical GABA levels by group, post hoc simple regression analyses were performed with significance adjusted for multiple comparisons using Bonferroni adjustments. Effects of depression severity on cortical GABA levels were assessed using ANCOVA controlling for age and sex. An α level of .05 was used to determine significance.

	8	9	10	11	12	13	14
	M/41	F/48	F/45	F/38	F/29	F/28	F/23
	Comorbid BPD	...	Anorexia nervosa	Atypical features, comorbid SP	...
1 MDE >20 y ago, antidepressant-induced mania, amphetamine abuse	36	Dysthymia, nondiscrete MDE 36	Multiple nondiscrete MDEs 21	1 MDE 24	Multiple nondiscrete MDEs 18	3 MDEs 6	...
Treatment resistant	1	0	3	0	1	1	0
	Treatment resistant	Treatment response, discontinued >3 y prior to study	Treatment resistant	1 Trial of a TCA	...

for age and sex ($F_{1,28} = 83.0, P < .001$). In this analysis both sex ($F_{1,28} = 19.4, P < .001$) and age ($F_{1,28} = 4.6, P = .04$) effects were significant. However, no significant diagnosis by sex or age interaction effect was found. **Figure 2** shows the complete separation of the control subject and depressed patient groups by occipital cortex GABA_(total) levels. Removing 2 patients who clinically required occasional doses of lorazepam or thioridazine from the analysis does not change the results ($F_{1,26} = 72.38, P < .001$).

Post hoc analysis of the sex effect on cortical GABA_(total) levels by 1-way ANCOVA covarying for age shows that both control and depressed female subjects have higher cortical GABA_(total) levels than their male counterparts, ($F_{1,15} = 11.4, P = .01$) and ($F_{1,11} = 11.06, P = .01$), respectively.

As noted above, the ANCOVA revealed significant age effects on cortical GABA_(total) levels in the total sample, yet no significant correlation of age and cortical GABA_(total) was seen within the 4 individual groups when split by diagno-

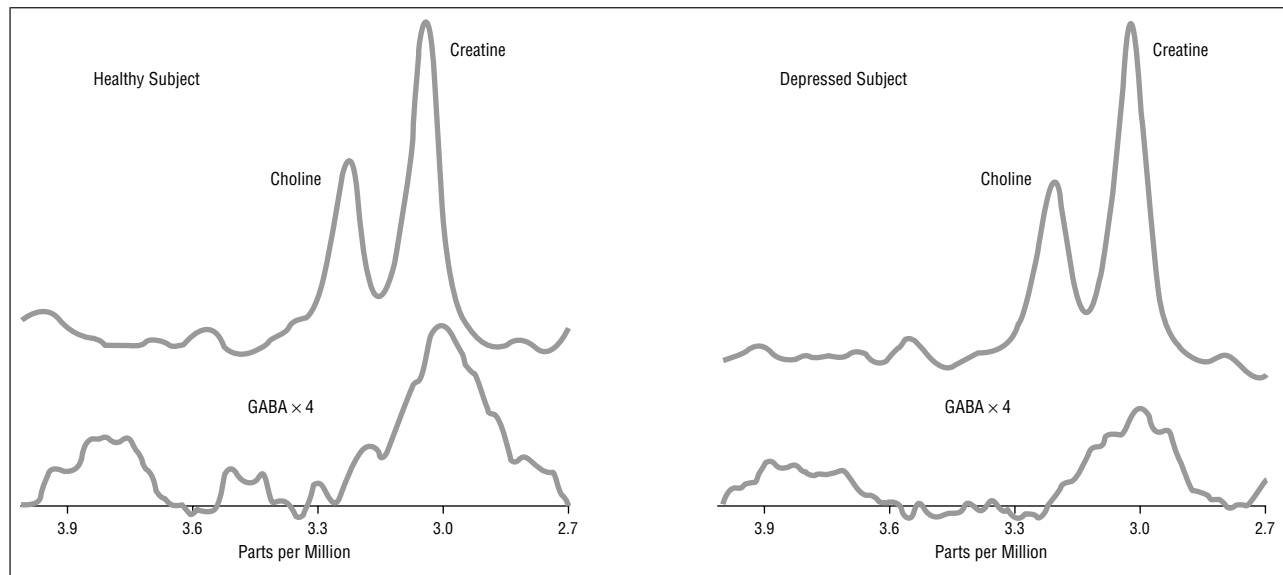


Figure 1. Representative spectra from a healthy control subject (left) and that of a depressed subject (right). The top spectrum for each subject depicts an unedited proton magnetic resonance spectroscopy spectrum. The lower spectrum illustrates a difference spectrum obtained using the delays alternating with nutations for tailored excitations editing pulse.

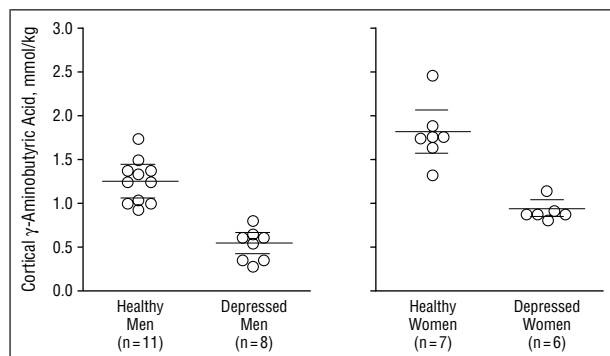


Figure 2. Individual subjects' proton magnetic resonance spectroscopy determined cortical γ -aminobutyric acid levels in brain tissue with means and 95% confidence intervals displayed.

sis and sex (healthy control subjects: men [$n = 11$, $r = -0.4$], women [$n = 7$, $r = -0.5$]; depressed patients: men [$n = 8$, $r = -0.1$], women [$n = 6$, $r = -0.4$]). The ANCOVA covarying for sex and age also did not reveal significant severity effects, as measured by the Hamilton Depression Rating Scale, on cortical $GABA_{(total)}$ levels. Only the sex effect remains significant ($F_{1,10} = 7.0$, $P = .02$) in this analysis. However, the power of both of these analyses is considerably limited by the small sample sizes.

COMMENT

This study provides, to our knowledge, the first direct evidence of decreased cortical GABA concentrations in depressed patients. No overlap was observed between cortical GABA levels of depressed patients and sex-matched healthy control subjects. The finding of lower cortical GABA concentrations is consistent with previous studies reporting lower GABA levels in the plasma and CSF of depressed individuals.^{14-17,32} However, to date the investigation remains limited to the region of the occipital cortex, a region not previously thought to be directly related to the pathophysiological

cal processes associated with major depression. Future research is needed to determine if the decreased occipital cortex GABA levels are an integral component of the pathophysiological processes responsible for the depressive symptoms or whether decreased levels reflect secondary consequences of other processes underlying depression.

Although limited by a small sample size, this study did not find a significant relationship between severity of depression and cortical GABA levels, consistent with several previous CSF studies.^{14,15,17} In contrast to these reports, Gerner et al¹⁶ did report a significant negative correlation between CSF GABA levels and severity of depression using a sample of 29 unipolar patients.

The mechanisms contributing to reduced cortical GABA levels in depressed patients are currently unknown. Decreased total GABA levels could reflect reductions in GABA synthesis arising from decreased glutamatergic stimulation of metabolic activity and reduced concentrations of substrate for GABA synthesis.³³⁻³⁵ The decreased synthesis could also reflect changes in glutamic acid decarboxylase activity. Several environmental, genetic, and immunological factors may contribute to the altered regulation of glutamic acid decarboxylase activity in these depressed patients.³⁵⁻³⁷ Alternatively, reduced GABA levels might reflect a relative deficit in glutamic acid decarboxylase activity due to increased GABA degradation.

Altered levels of homocarnosine could also contribute to the observed differences in the level of $GABA_{(total)}$. Homocarnosine is a GABA-containing dipeptide (GABA + histidine) with putative physiological functions.³⁸ The $GABA_{(total)}$ concentrations reported in our current study contain both GABA and homocarnosine levels. Thus, the lower levels measured in depressed patients could be due in part to reductions in homocarnosine. New proton magnetic resonance spectroscopy protocols³⁹ capable of isolating homocarnosine from the GABA peak will provide more information on the contributions of cortical homocarnosine levels to these findings.

Cortical GABA levels were higher in women than men, and they tended to decrease with advancing age. Studies of CSF GABA levels have inconsistently reported sex and age differences.^{16,18,40} Additional studies will be needed to replicate the preliminary findings of age and sex effects. Furthermore, it will be important to evaluate and control for potentially confounding variables such as cortical atrophy, altered gray-white matter ratios, altered creatine, metabolite, and homocarnosine levels in future analyses.

In summary, for the first time we have shown that cortical GABA levels are significantly lower in depressed patients relative to healthy control subjects. This finding was highly consistent among depressed subjects and was not significantly altered by the interaction of age or sex. Additional research is required to understand the pathophysiological and therapeutic significance of the altered cortical GABA levels in association with major depressive disorder.

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