

Magnetic Resonance Spectroscopy Studies of GABA in Neuropsychiatric Disorders

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Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system and is integral to managing brain excitability. GABA concentrations vary according to age, gender, and brain region. Magnetic resonance spectroscopy (MRS), with editing or with localized 2-dimensional chemical shift methods, can measure GABA levels in vivo, ex vivo, or in vitro, particularly at ultra-high magnetic field strengths. Proton (^1H) MRS studies have found reduced or abnormal GABA concentrations in several neuropsychiatric disorders, including epilepsy, anxiety disorders, major depression, and drug addiction. Disorders with low GABA levels may be treated by augmentation of GABAergic function, such as by medications that block the degradation or reuptake of GABA. Examples of such a rational therapeutic approach include anticonvulsants that elevate brain GABA levels and are effective for the treatment of epilepsy and anxiety disorder.

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GENERAL GABA PHYSIOLOGY

Gamma-aminobutyric acid (GABA) is synthesized in neurons from glutamine, with glutamate as an intermediate step, via glutamic acid decarboxylase and the co-factor pyridoxal phosphate. In addition, released GABA is taken up by glial cells, metabolized by GABA-transaminase, and enters the tricarboxylic acid cycle, which will eventually yield glutamate, which will be converted into glutamine by glutamine synthetase. The glial glutamine then can be transported back into the neurons for synthesis of new GABA. There are at least 2 GABA pools within the neuron: cytoplasmic and vesicular.¹

The synaptic effects of GABA are mediated through 2 major receptor subtypes, GABA_A and GABA_B. GABA_A receptors inhibit neurons and are crucial to controlling brain excitability. They house recognition sites for benzodiazepines, which are naturally occurring in the central nervous system as well as synthesized as psychotropic medications. Since GABA_A receptors also bind to other chemicals, including neuroactive steroids, ethanol, and anesthetics, the action of GABA_A receptors is modulated by a number of endogenous and exogenous ligands. GABA_B receptors are guanine-nucleotide-binding protein-coupled

receptors. Though little understood, GABA_B receptors are thought to modulate and inhibit the generation of excitatory postsynaptic potentials and long-term potentiation in the hippocampus and in the mesolimbic dopaminergic neurons.²

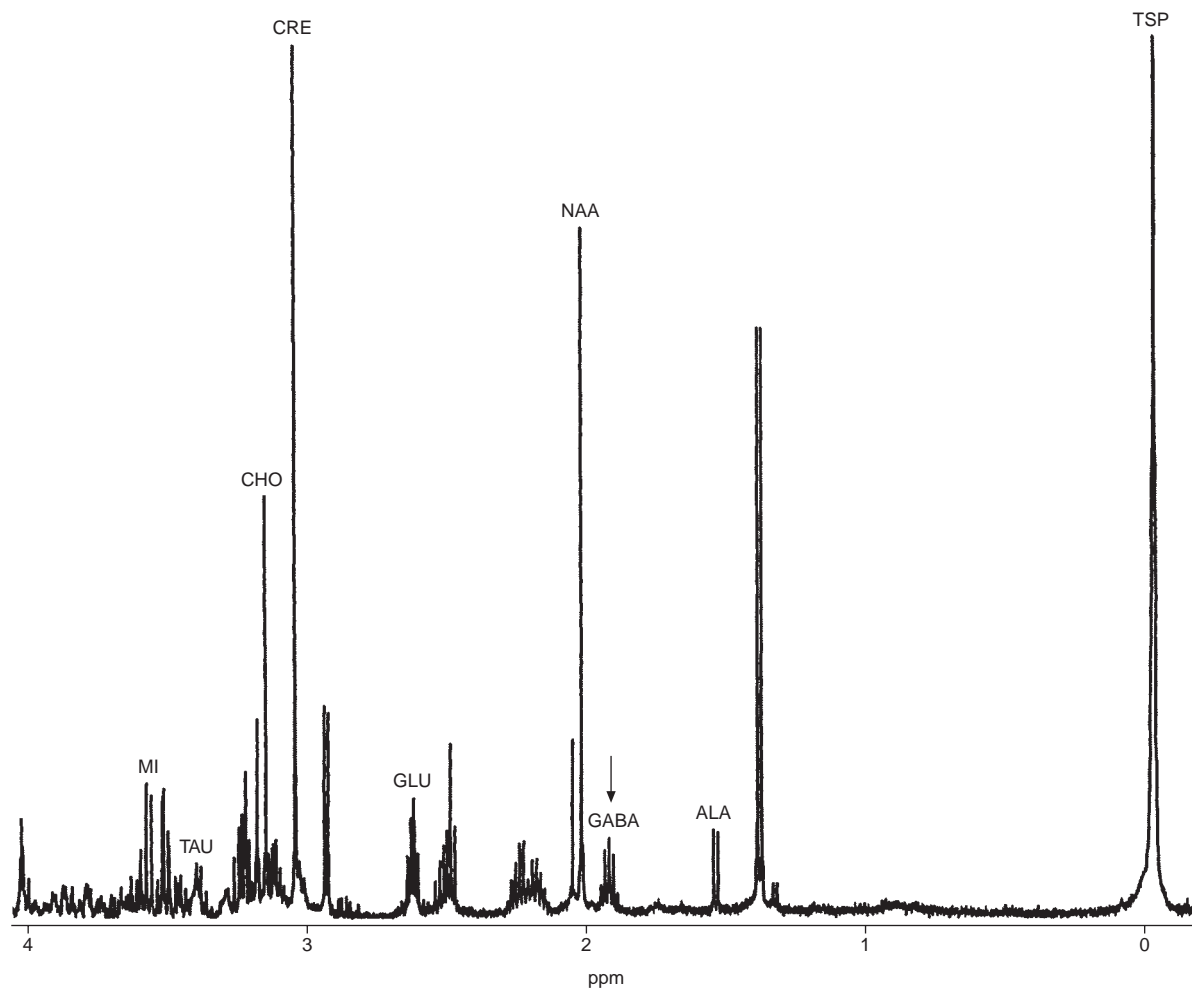
In the healthy human brain, GABA concentrations range from 0.5 to 1.4 $\mu\text{mol}/\text{cm}^3$.³ GABAergic neurons are widely distributed and have been shown to represent 10% to 40% of nerve terminals in the cerebral cortex, substantia nigra, and hippocampus of nonhuman primates.⁴ It has been estimated that as many as 75% of all synapses within the central nervous system are GABAergic.⁵ However, the human brain is chemically heterogeneous, and many metabolite concentrations, including GABA, vary by brain region, sex, and age. Although no accurate measurements of regional GABA levels have been performed in the living human brain, preclinical studies using either magnetic resonance spectroscopy (MRS) or high-performance liquid chromatography (HPLC), or both, found regional variations in GABA concentrations in the rat brain.^{6,7} In addition, female rats had higher GABA concentrations in the frontal cortex, and both sexes had higher GABA concentrations in the striatum compared with the frontal cortex and hippocampus.⁸

MAGNETIC RESONANCE SPECTROSCOPY: METHODOLOGICAL CONSIDERATIONS

Magnetic resonance spectroscopy provides a noninvasive means to identify and measure metabolites in vivo, ex vivo, or in vitro, especially metabolites that are present in relatively high concentrations in the brain. It is grounded in the same technology as magnetic resonance imaging

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Figure 1. Characteristic ^1H -MRS From an Ex Vivo Study of Rat Brain Cortex Extract^a

^aThe spectrum was acquired on a 500-MHz (11.7-T) nuclear magnetic resonance spectrometer. Note the well-delineated GABA resonances at 1.90–1.98 ppm (see arrow).

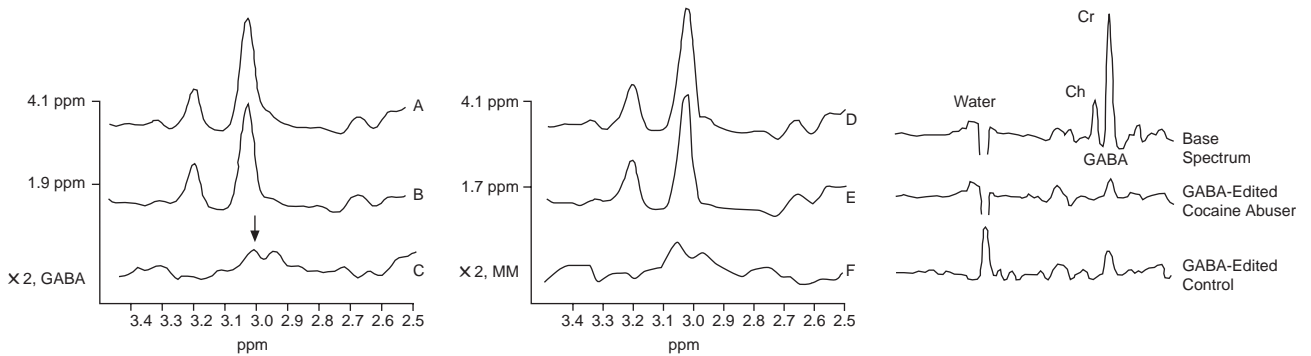
Abbreviations: ALA = alanine, CHO = choline compounds, CRE = total creatine, GABA = γ -aminobutyric acid, GLU = glutamate,

^1H -MRS = ^1H -magnetic resonance spectroscopy, MI = myoinositol, NAA = N-acetylaspartate, TAU = taurine, TSP = trimethyl-silyl-propionic acid.

(MRI) and uses strong magnets and radio-frequency pulses that excite atomic nuclei and measure differences in resonance frequency due to the differing chemical structure of various chemical compounds. Since the first demonstration of in vivo MRS in humans in the early 1980s, technological and methodological improvements have enabled quantitative and regional neurochemical measurements in numerous healthy and disease states. Assessment of regional chemical concentrations may aid in the diagnosis of a disease, allow evaluation of disease severity, or provide surrogate markers for monitoring treatment effects. Although chemicals containing other nuclei (e.g., phosphorous-31, carbon-13, lithium-7, and fluorine-19) can also be measured, ^1H -MRS is most commonly used in the clinical setting and has been approved by the U.S. Food and Drug Administration for clinical use since 1998 (CPT-4 code 76390).

Because the concentration of GABA is near the lower limit of detection by ^1H -MRS, it is very difficult to measure in vivo. The frequency location of the GABA peaks tends to be obscured by other overlapping metabolite peaks of higher concentrations, particularly by the creatine spectral peak. However, a number of specialized techniques can be used to enhance the visibility of the GABA peaks in the ^1H -MR spectrum. For example, ultra-high magnetic field improves spatial and spectral resolution (Figure 1). Only limited spectral resolution is possible with in vivo measurements at the common clinical magnetic resonance (MR) field strength of 1.5 T; however, highly selective editing techniques allow near-complete resolution of GABA peaks by subtracting out the confounding peaks or macromolecule contaminations^{3,9,10} (Figure 2). Localized 2-dimensional (2-D) chemical shift-correlated MR spectroscopic sequences, unlike editing

Figure 2. (left and middle) ^1H -MR Spectra Showing the Special Editing Techniques Needed to Measure Brain GABA Level In Vivo (see arrow)^a and (right) Application of This Optimized Editing Technique to the Study of Cocaine Abuse^b



^aFigure courtesy of Hoby Hetherington, Ph.D., modified from Hetherington et al.⁹ Left column: A and B represent spectra acquired with inversion pulses centered at 4.1 and 1.9 ppm, and C (vertical scale increased by 2) represents the subtraction of A and B. Right column: D through F show spectra optimized for editing of the macromolecules (MM). All spectra were obtained on a 4.1-T magnetic resonance scanner.

^bFigure courtesy of Hoby Hetherington, Ph.D., modified from Hetherington et al.⁶³ Note the lower GABA level in the cocaine abuser compared with the control subject.

Abbreviations: Ch = choline compounds, Cr = total creatine, GABA = γ -aminobutyric acid, ^1H -MR = ^1H -magnetic resonance.

techniques that target one metabolite at a time, can resolve many overlapping peaks nonselectively, with better dispersion of several metabolite peaks and improved spectral assignment.¹¹ Other techniques being developed to improve the detection of GABA include multiple quantum filtering techniques^{12,13} and carbon-13 (^{13}C) MRS, which involves the intravenous administration of non-radioactive ^{13}C -labeled glucose to measure regional glucose incorporation into glutamate, and then into GABA.¹⁴

MRS STUDIES OF GABA IN EPILEPSY

Since GABA is the major inhibitory neurotransmitter, abnormalities in the GABAergic system have long been implicated in the pathogenesis of epilepsy, a disorder of hyperexcitability. Strikingly abnormal GABA concentrations have been documented in some patients with intractable epilepsy. An *ex vivo* ^1H -MRS study of brain biopsies found 160% higher GABA levels in tuberose sclerosis patients with epilepsy and 340% higher GABA levels in patients with epilepsy due to cortical dysplasia compared with nonepileptic controls.¹⁵ Despite maintenance on treatment with anticonvulsants, both of these patient groups had intractable seizures that did not correlate with the GABA levels. In contrast, with *in vivo* measurements, patients with poorer seizure control tend to have lower GABA levels. One study found that juvenile myoclonic epilepsy (JME) patients had GABA levels (referenced to total creatine) 40% lower than normal controls and 30% lower than patients with refractory complex partial seizures (CPS) (Table 1)¹⁶; these JME patients had excellent seizure control despite the low GABA levels, whereas poorer seizure control in CPS patients was associated with lower GABA level. Therefore, although GABA levels are

abnormal in some epilepsy patients, other factors are very likely involved in the pathogenesis of seizures. To further assess the relationship between seizure control and brain GABA levels, Petroff et al. found that brain GABA levels measured with *in vivo* ^1H -MRS in epilepsy patients rose rapidly, within 1 to 24 hours, after administration of topiramate¹⁷ or vigabatrin,¹⁸ and the increased GABA levels correlated with improved seizure control in the vigabatrin study.¹⁹ Topiramate enhances GABA_A receptor-mediated chloride flux whereas vigabatrin is an irreversible GABA transaminase inhibitor; both drugs potentiate GABA activity and have shown efficacy for seizure control. Taken together, these studies further support the role of GABA in the maintenance of seizure control.

NEUROIMAGING STUDIES OF GABA IN ANXIETY

Benzodiazepines, which are both anticonvulsant and anxiolytic, increase the affinity of rat brain receptors for GABA by binding to sites on the GABA_A receptor complex.²⁰ Stimulated GABAergic function is considered anxiolytic, while inhibited GABAergic function is considered anxiogenic. Therefore, benzodiazepines are frequently and successfully used to treat panic and other anxiety disorders. However, individuals who suffer from anxiety disorders may have a GABA_A receptor dysfunction that prevents adequate benzodiazepine binding. This is based in part on the observation that individuals with anxiety disorders display a diminished response to exogenous benzodiazepine resulting in what might be described as an innate higher tolerance for them.²¹ Several studies have assessed the possibility of reduced sensitivity to benzodiazepine in patients with anxiety or panic disorders. Global reduction in benzodiazepine binding sites in

Table 1. In Vivo ¹H-MRS Studies Measuring GABA Levels in Neuropsychiatric Disorders

| Authors and Year | Patients and Subjects | MRS Methods and Brain Region(s) | Findings ^a |
|--|--|--|---|
| Sanacora et al, ³³ 1999 | Depression (N = 14), healthy controls (N = 18) | 2-T scanner, J-editing; occipital cortex | Depressed patients (DSM-IV diagnosis) had 52% lower mean GABA than controls |
| Behar et al, ⁴⁸ 1999 | Alcohol dependence (N = 5), hepatic encephalopathy (N = 5), healthy controls (N = 10) | 2-T scanner, J-editing; occipital cortex | Hepatic encephalopathy patients had 25% lower GABA than controls. Alcohol-dependent patients had 25% lower GABA than controls |
| Levy et al, ⁵² 1999 | Stiff-man syndrome (N = 8), healthy controls (N = 17) | 1.5-T scanner, 2-D J-resolved; occipital, putamen, and motor regions | GABA/creatinine is 18% (occipital) and 30%–40% (sensory-motor) lower in patients with stiff-man syndrome compared with controls |
| Levy and Hallett, ⁵³ 2002 | Focal dystonia ("writer's cramp," N = 7), healthy controls (N = 17) | 1.5-T scanner, 2-D J-resolved; occipital, putamen and motor regions | GABA/creatinine is 35% (putamen) and 42% (motor cortex) lower on the contralateral (left) side to the focal dystonia (all right-sided) compared with controls |
| Ke et al, ⁴⁹ 2001 | Cocaine abuse (N = 37), healthy controls (N = 10) | 1.5-T scanner, 2-D J-resolved; frontal region | 10%–20% lower GABA in dorsal lateral prefrontal cortex of cocaine users compared with controls |
| Hetherington et al, ⁶³ 2000 | Cocaine abuse (N = 10), healthy controls (N = 6) | 4-T scanner, J-editing; occipital cortex | 23% lower GABA in occipital cortex of cocaine abusers compared with controls |
| Petroff et al, ¹⁶ 2001 | Complex partial seizures (CPS, N = 12), juvenile myoclonic epilepsy (JME, N = 14), healthy controls (N = 18) | 2-T scanner, J-editing; occipital cortex | JME patients had 40% lower GABA and normal homocarnosine compared with controls. CPS patients had 10% lower GABA and 24% lower homocarnosine compared with controls |
| Goddard et al, ²⁸ 2001 | Panic disorder (N = 14), healthy controls (N = 14) | 2-T scanner, J-editing; occipital cortex | Compared with controls, panic disorder patients (DSM-IV diagnosis, with or without agoraphobia) had 22% reduction in GABA plus homocarnosine, which did not correlate with measures of illness or anxiety state |
| Epperson et al, ³⁴ 2001 | Premenstrual dysphoric disorder (PMDD, N = 7), healthy women (N = 9) | 2-T scanner, J-editing; occipital cortex | GABA level is lower at the follicular phase but higher in the mid-luteal phase of women with PMDD; in contrast, the GABA levels in the healthy women are higher in the follicular phase than the mid-luteal phase |

^aAll GABA levels measured used total creatine as an internal reference and assumed a stable creatine level of 9 mmol/kg or 7.1 mmol/kg in all subjects.

Abbreviations: GABA = γ -aminobutyric acid, ¹H-MRS = ¹H-magnetic resonance spectroscopy.

patients with panic disorder, including in brain regions postulated to mediate anxiety (e.g., frontal and temporal regions), has been shown by several single photon emission computed tomography studies,^{22–25} as well as a positron emission tomography (PET) study.²⁶ However, not all PET studies observed reductions in benzodiazepine binding.²⁷ In mice, dysfunction of benzodiazepine receptors is directly linked to neophobic behaviors that resemble agoraphobia in humans.²⁸ An alternative explanation may be that levels of endogenous benzodiazepine or GABA may be abnormally low in patients with anxiety disorders.

Several ¹H-MRS studies found greater increase in brain lactate in response to hyperventilation or to lactate infusion in patients with panic disorder (procedures known to induce panic attacks in these patients).^{29,30} One study even found gabapentin to be effective in blocking the lactate-induced panic response but did not alter the magnitude or time course of an abnormal brain lactate response to the infusion.³¹ Only one ¹H-MRS study, by Goddard et al.,²⁸ has measured GABA levels in unmedicated patients with panic disorder (Table 1). Although the frontal lobe is more frequently linked to processes of anxiety, methodological limitations and the use of a surface coil to maximize signal detection restricted the measure-

ments to the occipital lobe in this study. The majority (12 of 14) of these patients with panic disorder had lower occipital GABA levels (reference to total creatine), with a group mean reduction of 22%, compared with healthy controls matched for sex and age. This study supports the view that reduced GABA may be related to anxiety disorders.

MRS STUDIES OF GABA IN DEPRESSIVE OR MOOD DISORDERS

Anticonvulsants that elevate GABA frequently have antidepressant properties as well as anxiolytic ones. Conversely, many antidepressants have GABAergic effects. Dysregulation of GABAergic neurotransmission is implicated in depression for several reasons. As reviewed by Sanacora and colleagues,³² preclinical studies have shown stress-induced changes in GABAergic function, including decreased GABA concentrations and decreased GABA_A receptor binding, and stress is widely considered pathogenic to depression. In addition, behavioral models of depression in animals can be manipulated by GABA agonists (anxiolytic) and antagonists (anxiogenic). Furthermore, brains of depressed patients show GABAergic abnormalities compared with controls; all studies to date have found

at least a trend toward decreased cerebrospinal fluid GABA in depressed subjects. These data collectively suggest that GABA levels may be abnormal in the brains of patients with depression or mood disorders.

In the first in vivo MRS study to evaluate brain GABA levels in depressed patients, Sanacora and colleagues found a 52% reduction in GABA levels (referenced to total creatine) in the occipital cortex of nonmedicated patients with major depression compared with healthy controls (Table 1).³³ Another preliminary study found that women with premenstrual dysphoric disorder (PMDD), who are at risk for episodes of major depression, had higher GABA levels during the mid-luteal phase but lower GABA levels during the follicular phase of their menstrual cycles, which is the inverse trend compared with the GABA levels in healthy control women (Table 1).³⁴ These findings demonstrate the importance of matching not only for sex in GABA measurements, but also for the phase of the menstrual cycle when evaluating female subjects. Currently, the mechanisms for these abnormal GABA levels are unknown; these changes could be due to abnormalities in GABA synthesis or degradation, or both. These 2 studies further suggest that abnormal GABA levels may contribute to the pathogenesis of depression or mood disorders.

MRS STUDIES OF GABA IN DRUG ABUSE

Emerging clinical data indicate that decreased GABAergic function may represent a major etiologic step in the development and maintenance of the addictive state, and medications that affect the GABA system may be useful as treatments for addiction. For example, reduced plasma and cerebrospinal fluid GABA,^{35,36} as well as lower metabolic response to lorazepam, have been observed in the alcoholic withdrawal state.³⁷ Seizures associated with alcohol withdrawal or cocaine intoxications are responsive to, and hence treated with, benzodiazepines but not phenytoin. Preliminary clinical data show that baclofen, a GABA_B agonist, decreased craving and use of cocaine³⁸ and alcohol,³⁹ but not of nicotine.²

Numerous preclinical studies over the past decade also demonstrated that GABA neurons, via GABA_B receptors, can modulate and inhibit the mesolimbic dopamine system,⁴⁰ which is associated with the reinforcing effects of and craving for abused drugs.⁴¹ PET studies in baboons and microdialysis in rodents have shown that gamma-vinyl GABA (GVG, or vigabatrin), a GABA transaminase inhibitor, significantly reduced cocaine-induced extracellular dopamine release in the nucleus accumbens.^{42,43} The reduction in dopamine release and in drug consumption by GVG is even more potent for ethanol than for cocaine.⁴⁴ GVG also blocks the reinforcing effects of heroin, cocaine, and/or ethanol in rodents to self-administer

the drug or to associate the drug with an environmental cue.^{44,45} Furthermore, GABA_A receptor agonists, including muscimol and gaboxadol, selectively enhance ethanol consumption, while the GABA_A antagonist bicuculline blocked the enhancement.⁴⁶ In contrast, baclofen, a GABA_B receptor agonist, significantly reduced methamphetamine self-administration in rats.⁴⁷ Therefore, not only has GABAergic function been shown to be abnormal in various addictive states, pharmacologic manipulations using this knowledge can alter the reinforcing effects of drugs and drug-seeking behavior. This approach might significantly improve the treatment of addiction in humans.

Only a few studies have begun to evaluate the GABAergic system in humans with drug dependence (Table 1). A preliminary in vivo ¹H-MRS study of 5 recently detoxified alcoholics showed a 35% decrease in combined GABA and homocarnosine, an inhibitory neuromodulator synthesized in subgroups of GABA neurons.⁴⁸ Two ¹H-MRS studies have evaluated cocaine abusers and found 23% lower GABA levels (referenced to total creatine) in the occipital cortex (Figure 2)⁶³ and 24% lower GABA levels (also referenced to total creatine) in the dorsal lateral prefrontal region,⁴⁹ compared with levels in the controls. Since all of these studies were referenced to the total creatine, which has been shown to be elevated in cocaine users,^{50,51} the decrease in the GABA measurements may also reflect the associated increased creatine. Future studies need to additionally measure the total creatine to better assess the changes in GABA concentration in individuals with addiction. These preliminary studies, nevertheless, suggest that lower levels of GABA in alcoholics and cocaine users may contribute to the addictive behavior.

¹H-MRS STUDIES IN OTHER NEUROPSYCHIATRIC DISORDERS

The ability to measure brain GABA in vivo has prompted additional research in other neuropsychiatric disorders that have probable GABAergic abnormalities based on postmortem studies or disease mechanisms. Decreased GABA (relative to total creatine) has been observed in patients with stiff-person syndrome (by 40% in the sensorimotor region)⁵² and with focal dystonia (by 35% in the lenticular nuclei and 42% in the contralateral motor cortex)⁵³ (Table 1). One study also evaluated patients with hepatic encephalopathy and found 26% decreased GABA + homocarnosine (relative to total creatine) levels⁴⁸ (Table 1). Since many other neuropsychiatric diseases, such as schizophrenia, Huntington's disease, Parkinson's disease, attention-deficit/hyperactivity disorder, and Tourette's syndrome, have established neurotransmitter abnormalities that are related directly or indirectly to the GABAergic system, future investigations of these diseases with in vivo MRS should lead to a better understanding of the role of GABA in these disorders.

Table 2. In Vivo ¹H-MRS Studies Showing Modulation of Brain GABA Levels With GABAergic Medications

| Authors and Year | Subjects | Drug(s) Given | Mechanism(s) of Action | Findings |
|---|---|---|--|---|
| Studies in epilepsy patients | | | | |
| Petroff et al, ¹⁹ 1996 | Complex partial seizures (CPS, N = 18), healthy controls (N = 15) | Vigabatrin (3–6 g/d) | GABA transaminase inhibitor | GABA levels in CPS patients who received vigabatrin (3–4 g/d) increased 2-fold compared with controls, but failed to increase further with 6 g/d. Brain GABA declined over 1–2 years at constant dose (6 g/d) |
| Petroff et al, ¹⁸ 1996 | Complex partial seizures (N = 7) | Vigabatrin (50 mg/kg), single dose | GABA transaminase inhibitor | Compared with baseline, GABA level increased ~40% within 2 hours of a 50-mg/kg oral dose of vigabatrin, increased further next day, but declined at days 5 and 8 |
| Petroff et al, ¹⁷ 2001 | Complex partial seizures (N = 15) | Topiramate (100 mg), single dose | Enhance GABA _A receptor–mediated chloride flux | Compared to baseline, brain GABA rose rapidly in 1 h, doubled in 4 h, and remained elevated after 24 h |
| Studies in healthy humans and rats | | | | |
| Kuzniecky et al, ⁶¹ 1998 | Healthy volunteers (N = 6) | Topiramate (3 mg/kg), single dose | Enhance GABA _A receptor–mediated chloride flux | Topiramate raised brain GABA levels by 72% at 3 h and by 64% at 6 h compared with baseline |
| Mueller et al, ⁵⁴ 2001 | Healthy volunteers (N = 8) | Pyridoxal 5'-phosphate (PP, or vitamin B6); vigabatrin (1–4 g/d) | PP: co-factor for glutamic acid decarboxylase; vigabatrin: GABA transaminase inhibitor | Monotherapy with vitamin B6 alone did not change the GABA/creatinine ratio. Vigabatrin alone increased the GABA/creatinine ratio by 11%. The combination of PP and vigabatrin varied depending on the sequence of the drugs and dose of vigabatrin |
| Kuzniecky et al, ⁶² 2002 | Healthy volunteers (N = 17) | Target doses: topiramate (4 g/d), gabapentin (2.4 g/d), lamotrigine (0.5 g/d) | Topiramate: enhance GABA _A receptor mediated chloride flux; gabapentin: unknown; lamotrigine: unknown | Brain GABA level increased acutely with topiramate (70% at 3–6 h) and with gabapentin (48% at 6 h) but not with lamotrigine. At 4 wks, with target doses, GABA levels were increased with all 3 drugs (topiramate 46%, gabapentin 25%, and lamotrigine 25%) |
| de Graaf et al, ⁵⁶ 2001 | Healthy adult male rats (N = 15) | Vigabatrin (175–700 mg/kg) | GABA transaminase inhibitor | Vigabatrin led to a dose- and time-dependent increase of 2–6 mM in brain GABA in 1–5 h. GABA transaminase activity was inhibited by > 60% at all doses |
| Welch et al, ⁵⁷ 2001 | Healthy adult male rats: treated (N = 4), untreated (N = 10) | Vigabatrin (200 mg/kg) | GABA transaminase inhibitor | Vigabatrin increased GABA/creatinine (+160%) and glutamate + glutamine (+28%) |

Abbreviations: GABA = γ -aminobutyric acid, ¹H-MRS = ¹H-magnetic resonance spectroscopy.

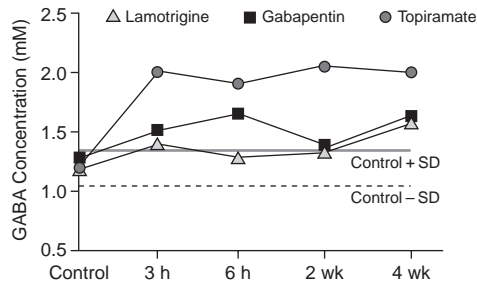
MODULATION OF GABA LEVELS WITH MEDICATIONS

Brain GABA levels can be modulated by pharmacologic agents that block the enzymatic degradation, or the reuptake, of GABA. As stated, agents that enhance GABA neurotransmission generally have anticonvulsant activity, as well as antidepressant and/or anxiolytic qualities. Several clinical and preclinical studies have evaluated in vivo brain GABA levels after acute and chronic administration of anticonvulsants (Table 2). Vigabatrin is effective for focal seizures and infantile spasms and has been shown to rapidly elevate brain GABA levels (relative to total creatine) in healthy human subjects⁵⁴ and in epileptic patients.⁵⁵ Similarly, elevated GABA levels after vigabatrin administration have been shown in rodents using a J-editing technique⁵⁶ and a 2-D MRS technique.⁵⁷ One MRS study also evaluated brain GABA levels in epileptic patients who developed visual problems associated with vigabatrin, and those who had no such problems, and found no difference in their GABA levels.⁵⁸ Gabaculine, another GABA transaminase inhibitor, also raised both

intracellular (500%) and extracellular GABA (50%) within 1 hour, and the levels continued to climb over the next 6 hours.⁵⁹ Among GABA uptake inhibitors, tiagabine crosses the blood-brain barrier most readily. Rats given tiagabine, at doses known to inhibit certain tonic seizures, showed significantly increased extracellular levels of GABA in the ventral pallidum in a dose-dependent manner.⁶⁰ A dose of 11.5 mg/kg of tiagabine increased extracellular GABA by 280% the basal level; GABA increase reached 350% the basal level at a dose of 21.0 mg/kg of tiagabine. Further, 11.5 mg/kg of tiagabine caused extracellular levels of GABA in the globus pallidus to increase 240% in 20–40 minutes perfusate, with gradual decline.

Topiramate, a relatively new anticonvulsant that potentiates GABA_A receptor–mediated activity, also elevated brain GABA by 70% acutely (1–4 hours) after a single dose in healthy subjects⁶¹ and in patients with complex partial seizures,¹⁷ and the levels remained elevated at 24 hours in the patients (Table 2).¹⁷ Another recent ¹H-MRS study further evaluated the acute effects of 2 additional anticonvulsants in healthy volunteers and found that, although to a lesser degree than with topiramate, brain

Figure 3. GABA Levels Both Increased Acutely and Remained Elevated at 4 Weeks After Administration of Lamotrigine, Gabapentin, and Topiramate^a



^aFigure courtesy of Hoby Hetherington, Ph.D., based on data reported in Kuzniecky et al.⁶²

Abbreviation: GABA = γ -aminobutyric acid.

GABA was elevated 48% by gabapentin (at 6 hours), but not with lamotrigine (Figure 3).⁶² However, with long-term dosing after 4 weeks, all 3 drugs were associated with elevated brain GABA (topiramate 46%, gabapentin 25%, and lamotrigine 25%).⁶² The long-term effect with lamotrigine is unexpected since it is characterized as a sodium channel drug, similar to phenytoin and carbamazepine, but it appears to have an indirect effect on GABA. The mechanisms of action for these 3 drugs are not well understood; unlike for vigabatrin, no data support either inhibition of GABA transaminase or increased GABA synthesis. The acute and rapid elevation of GABA levels with topiramate and gabapentin suggest nonvesicular GABA release or other unknown mechanisms.⁶²

CONCLUSION AND FUTURE DIRECTIONS

All of the published clinical studies that measured GABA levels used total creatine as an internal reference and assumed that total creatine is unchanged even in the disease states. However, since creatine can vary depending on brain region and age and in numerous disease conditions, GABA concentration cannot be assessed accurately using total creatine as a reference. Therefore, future methodological developments are needed to further allow accurate measurements of brain GABA concentration or the rate of GABA synthesis.

The GABAergic system modulates both normal and pathologic responses in the central nervous system and is central to inhibiting brain excitability. GABA levels appear to be decreased in a variety of neurologic disorders, especially in those with symptoms of brain hyperexcitability, such as epilepsy. Brain hyperexcitability and low GABA concentrations are also linked to a variety of psychiatric disorders, including anxiety, depression, addiction, and possibly schizophrenia. Since brain GABA levels can now be measured with ¹H-MRS, which is

noninvasive and non-radioactive, future studies can employ this technique to evaluate brain disorders involving possible dysregulation of the GABAergic system. In addition, MRS will play an important role in monitoring the therapeutic effects of GABAergic agents, such as benzodiazepines, GABA transaminase inhibitors, and GABA reuptake inhibitors.

Drug names: baclofen (Lioresal and others), carbamazepine (Carbatrol, Tegretol, and others), gabapentin (Neurontin), lamotrigine (Lamictal), lorazepam (Ativan and others), phenytoin (Cerebyx, Dilantin, and others), tiagabine (Gabitril), topiramate (Topamax), vigabatrin (Sabril).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, baclofen is not approved by the Food and Drug Administration for decreased craving for cocaine and alcohol, lorazepam is not approved for alcohol withdrawal, and gabaculine, gaboxadol, and muscimol are not approved for human use in the United States.

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