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## REVIEW ARTICLE

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# GABA-Based Evaluation of Neurologic Conditions: MR Spectroscopy

**SUMMARY:** GABA serves as a major neurotransmitter of the brain and functions mainly to inhibit neural excitatory activity. Disruption of the GABAergic processes appears to occur in various neurologic and psychiatric conditions, including epilepsy, mood disorders, motor disorders such as focal dystonia and stiff-person syndrome, sleep disorders, neuroplasticity, and drug and alcohol dependence. These concentration differences may be ascertained by using MR spectroscopy to provide information on the concentration of different metabolites. This review briefly discusses advances in MR spectroscopy methods and explores the application of this technique to detect changes in GABA due to disease processes and medication-induced effects.

**ABBREVIATIONS** AED = antiepileptic drug; GABA =  $\gamma$ -aminobutyric acid; GABA<sub>A</sub>R =  $\gamma$ -amino butyric acid A receptor; GABA<sub>B</sub>R =  $\gamma$ -amino butyric acid B receptor; GABA-T = GABA transaminase; GAD = glutamic acid decarboxylase; J-PRESS = a combined 2D point-resolved spectroscopy sequence; SSRI = selective serotonin reuptake inhibitor

The importance of GABA first emerged from experimental work in the 1950s by Eugene Roberts, identified from extracts of mouse neuroblastoma; the primary inhibitory neurotransmitter activity of GABA was postulated only years after its discovery.<sup>1,2</sup> GABA is the major inhibitory neurotransmitter within the brain and accounts for almost half of synaptic activity.<sup>3</sup>

GABA arises from glutamic acid by GAD and is broken down by GABA-T. There are 2 major types of GABA receptors: GABA<sub>A</sub>R, which has a predominant inhibitory effect in the cortex, and GABA<sub>B</sub>R, which inhibits excitatory potentials and enables long-term potentiation in the hippocampal and mesolimbic regions.<sup>4</sup> Alterations in brain GABA concentrations and in GABAergic pathways are implicated in the pathophysiology of a number of neurologic disorders to be discussed in this review.

## Principles of GABA Measurement on MR Spectroscopy

Conventional MR spectroscopy techniques can presently assess, with a good degree of reliability, only a small number of metabolites in the human brain. The primary information from the MR spectra has been generally limited to the levels of the few largest peaks: Cr, Cho, NAA, and lactate. GABA appears much lower in concentration, with an average concentration of 1 mmol/L versus 5–10 mmol/L.<sup>5</sup> One of the earliest demonstrated detections of GABA in vivo by using MR spectroscopy occurred in the 1990s by Rothman et al.<sup>6</sup> More recently, additional various technical modifications have been introduced to recognize metabolites such as GABA, glutamine, glutamate, glucose, and others.<sup>7</sup> These attempts have not always been successful due to difficulties in extracting this

type of information from spectra with overlapping resonant peaks.

Another limitation of current MR spectroscopy methods concerns the difficulty of comparing levels of GABA among subjects or in disease states. One way in which researchers have addressed this concern is to express the GABA concentration relative to another metabolite such as Cr. Other problems inherent in MR spectroscopy are the imprecise nature of some ROIs selected to measure metabolites. These ROIs may include differing types of brain matter inadvertently through partial volume effects; gray matter contains a much greater concentration of GABA than white matter.<sup>8</sup> Moreover, regardless of the size of the ROI, MR spectroscopy cannot indicate whether the concentration of a metabolite measured lies intracellularly or extracellularly; therefore, decreased GABA, for instance, might result from decreased numbers of GABAergic neurons, smaller neurons, or decreased GABA extracellularly. GABA concentrations also may not reflect neurotransmitter flux or the number and activity of GABA receptors. The actual significance of each of these limitations is uncertain at present.

A comparison of conventional versus neurotransmitter (GABA) metabolite characteristics for MR spectroscopy is shown in the Table. In conventional spectroscopy, the usual metabolites, such as NAA, Cr, and Cho, usually have much greater signal intensity than metabolites such as GABA and other neurotransmitters and are much easier to measure. Also, they tend to vary much less than neurotransmitters temporally and across brain regions. Most important, neurotransmitters are more closely related to brain function, whereas the usual metabolites are more often associated with structural parameters. This becomes important in evaluating various neurologic disorders and the effect of therapies.

## Spectral Editing

Spectral editing sequences have been used to select out J-coupled metabolites from each other; however, only 1 metabolite at a time can be individually selected. A frequency-selective radio-frequency pulse can be applied to generate a spectrum that only depicts signals affected by the selective pulse.<sup>9,10</sup>

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### Comparison of conventional versus neurotransmitter (GABA) metabolite characteristics for MRS

Metabolite Characteristics	Conventional Metabolites (NAA, Cr, Cho)	Neurotransmitters (GABA)
Magnitude	Large	Small
Function	Structural	Physiologic
Spatial	Homogeneous	Regional
Temporal	Constant	Dynamic

Double-quantum filtered and other methods may afford greater editing but may be subject to signal-intensity loss<sup>11</sup>; there are also other spectral editing methods that are beyond the scope of this review.<sup>12-18</sup>

#### 2D MR Spectroscopy

2D proton MR spectroscopy offers the possibility of obtaining all the major cerebral metabolites *in vivo* in a localized acquisition.<sup>19-21</sup> Recent techniques to distinguish GABA from other molecules can use spectral editing and 2D uncoupling such as MEGA-PRESS (J-difference editing point resolved magnetic resonance spectroscopy), J-PRESS, and inner volume saturation as exemplified in Fig. 1.<sup>22,23</sup>

#### Clinical Uses of GABA MR Spectroscopy

Clinically, the ability to obtain cerebral metabolic information provides clinicians with a powerful tool to evaluate or serially follow-up diseases. Present measurements of certain cerebral metabolites, such as GABA, have previously been generally limited to measurements of concentration levels in the blood and CSF, but these are only an indirect reflection of brain levels. Furthermore, they cannot be localized to a particular anatomic region of the brain to assess localized metabolism or regional pathology. Direct MR spectroscopy brain measurements circumvent many of these problems and easily permit serial temporal quantitative assessment of disease progression and drug-mediated effects.

#### Investigation of GABA Physiology by Using MR Spectroscopy

Recent evidence supports the role of GABA in serving as a gateway for cortical activity. GABA reduction appears to allow increased excitatory activity and vascular reactivity.<sup>24-26</sup>

GABA may also allow synaptic plasticity and cortical reorganization. In a study of deafferentation, Levy et al<sup>27</sup> demonstrated rapid decreased GABA concentrations following initiation of a nerve block. This same concept of GABA reduction as an opening of a gate to allow for synaptogenesis is reinforced by experiments of motor learning tasks.

#### Conditions Involving GABA

##### Epilepsy

GABA dysfunction has long been postulated as a contributor to seizure activity—reduced GABA would be expected to allow unbridled excitatory neural activity. In line with this theory, antiepileptic medications generally have an effect on increasing GABAergic activity and decreasing CSF levels of GABA.<sup>28</sup> Moreover, antibodies to GAD have been detected in many groups of patients with seizure disorders; this autoim-

mune phenomenon would be expected to curtail GABA synthesis.<sup>29,30</sup> In patients with anti-GAD-antibody-positive epilepsy, compared with healthy controls, GABA levels are lower within the primary sensorimotor cortex.<sup>31</sup> An early study of GABA MR spectroscopy demonstrated that patients with more recent seizure recurrence had much lower concentrations than did those who had been symptom-free longer.<sup>32</sup> GABA is also reduced in the setting of juvenile myoclonic epilepsy and complex partial seizures.<sup>33,34</sup> Moreover, poorer seizure control in complex partial seizure disorder appears to correlate with decreased GABA levels.<sup>33</sup> These findings support the notion of decreased GABAergic function and the occurrence of epilepsy.

On the other hand, others have failed to find decreased GABA concentrations, even following resection of the abnormal seizure focus<sup>35</sup> or in idiopathic generalized epilepsy while finding elevations in glutamate and glutamine.<sup>36,37</sup> An abnormal cortex in seizure disorders may demonstrate marked GABA elevation, such as in cortical tubers.<sup>38</sup> It is clear from these divergent reports that there may be regional variance within different regions of the cortex in different seizure disorders that are still poorly characterized. *Ex vivo* spectroscopy experiments also contradict these findings, with the detection of increased levels of GABA on MR spectroscopy of brain biopsies from patients with intractable epilepsy.<sup>39-41</sup>

##### Motor Disorders

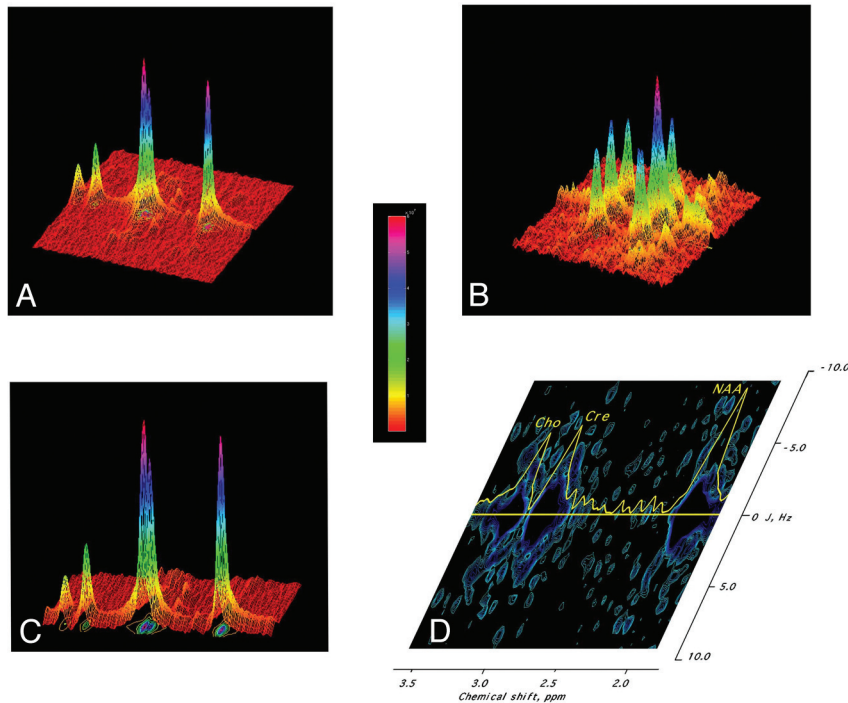
Stiff-person syndrome consists of muscle rigidity and episodic muscle spasms.<sup>42</sup> As in the case of epilepsy, autoantibodies to the GAD enzyme (GAD-65) have been detected.<sup>43-45</sup> Reduced CSF GABA levels suggest that decreased inhibitory activity leads to excessive cortical-directed muscle excitation.<sup>44</sup> On MR spectroscopy, Levy et al<sup>42</sup> reported prominent decreases in GABA in the brains of these patients.

Similarly, decreased inhibition by GABA may result in focal dystonia, such as in the case of writer's cramp.<sup>46</sup> This decrease in the amount of GABA is thought to encourage plasticity and perhaps lead to excessive plasticity and functional impairment.<sup>47</sup>

##### Mood and Anxiety Disorders

Mood disorders also appear to share the phenomenon of reduced GABA.<sup>48</sup> Patients with unmedicated major depressive disorder have demonstrably lower GABA levels within the dorsomedial/dorsal anterolateral prefrontal cortex<sup>49</sup> and occipital cortex.<sup>50</sup> GABAergic decreases have been noted in depressed subjects in both the occipital and anterior cingulate cortex.<sup>51</sup> Bipolar patients would be expected to share these brain chemistry changes, especially with demonstrated histologic loss of GABAergic neurons and decreased plasma GABA levels.<sup>52,53</sup>

Angiogenesis may involve GABAergic dysfunction, allowing increased neural excitability as suggested by the effectiveness of benzodiazepines as anxiolytics. Patients with panic disorder possess significantly lower GABA levels than controls.<sup>54</sup> Those patients on chronic anxiolytics also had decreased GABA concentrations in the occipital cortex and showed blunted responses to benzodiazepines, suggesting impaired GAD function.<sup>55</sup> On the other hand, patients with social anxiety disorder, while having significantly elevated glutamate



**Fig 1.** Example of 2D J-PRESS spectroscopy. *A*, 2D spectrum of a phantom containing NAA and Cr displayed in 3D, with the vertical axis being signal intensity; the horizontal axis, the chemical shift; and the oblique axis, the “decoupling” or J-dimension. Introduction of this second dimension provides spectra of greater resolution, as if a mountain range was visualized from above (2D spectrum) rather than just from its skyline (conventional 1D spectrum). The color bar denotes signal intensity. *B*, 2D spectrum of GABA shows the characteristic set of 3 vertical rows compatible with its spectroscopic structure of 2 triplets and 1 multiplet. A large central peak of GABA triplet ( $\alpha$ -Carbon Hydrogen [CH]) is shown. *C*, Projection of the 2D spectrum in *A* maps the individual peaks onto a contour plot. *D*, 2D spectroscopy contour plot of the human sensorimotor cortex. The horizontal axis represents chemical shift; the vertical axis represents the J-axis. The decoupled peaks of the metabolites can then be identified from their known assigned resonances. The 1D profile along the J = 0 axis is plotted in yellow. Large peaks occurring along the  $J_0$  axis ( $J_0$  subspectrum) at the characteristic chemical shifts of the major peaks of NAA (CH3 at 2.02 ppm), Cr (CH3 at 3.04 ppm), and Cho (CH3 at 3.2 ppm) are marked. The central peak of the GABA-CH2 resonance can be seen on  $J_0$  subspectrum (2.31 ppm), with side peaks corresponding to the triplet structure ( $\pm 7.3$  Hz).

and glutamine, showed no differences in GABA compared with healthy controls.<sup>56</sup>

In an elegant threat-of-shock experiment by using MR spectroscopy, Hasler et al<sup>57</sup> showed that healthy individuals demonstrate an average 18% reduction in prefrontal GABA from this acute stress scenario. Because anxiety is closely related to perceived threat, this study suggests that GABA mediates fear—a decrease in GABA might allow priming of a motor response to a feared threat.

### Schizophrenia

It is hypothesized that the cognitive impairments observed in schizophrenia may be related to decreased GABA levels resulting from pancortical decreased GAD transcription.<sup>58</sup> A recent MR spectroscopy study found that GABA is decreased within the visual cortex in patients with schizophrenia, reinforcing the idea of GABA disruption as the mechanism of loss of cognitive inhibition.<sup>59</sup> Tayoshi et al<sup>60</sup> found more GABA in those patients taking typical antipsychotics versus atypical antipsychotics. Thus, treatment effects may hamper the ability to detect GABA reductions in patients with schizophrenia on medication.

### Alcoholism and Drug Addiction

The importance of GABA in alcoholism is evident in the clinical utility of benzodiazepines in mitigating seizure activity in the setting of acute withdrawal.<sup>61</sup> Similarly, baclofen (a GABA<sub>B</sub>R agonist) appears to reduce craving and consumption

of alcohol through a GABA-related mechanism.<sup>62</sup> Alcohol appears to facilitate GABAergic activity at the GABA<sub>A</sub>R; therefore, it is suggested that GABA levels in chronic alcohol use would be lower.<sup>61,63</sup> MR spectroscopy of alcohol-dependent subjects supports the concept of alcohol-induced GABAergic modification. GABA plus homocarnosine was significantly lower in patients with recently treated alcoholic hepatic encephalopathy and those recently detoxified compared with healthy controls.<sup>64</sup> In another study, decreased levels of GABA in alcohol-dependent individuals versus healthy controls were not found<sup>65</sup>; this discrepancy may be related to the time course of alcohol withdrawal. In fact, GABA levels were found to be normal shortly after withdrawal and then decreased after a month of sobriety.<sup>66</sup>

Cocaine users share similar findings as those seen in alcoholics: Cerebral GABA levels were significantly reduced in several studies when users were compared with controls.<sup>67,68</sup> Reductions within the prefrontal cortex explain disinhibition and impaired impulse control seen with cocaine use.

### Sleep Disorders

GABA has been implicated in sleep disorders, with benzodiazepines having demonstrable effectiveness in treating insomnia. This theory is backed by the finding of substantially reduced global GABA levels in chronic primary insomnia.<sup>69</sup> Kakeda et al<sup>70</sup> noted a substantial reduction in the GABA/Cr ratio in the frontal lobes of alternate-shift workers by using MR spectroscopy.

Conversely, young patients with narcolepsy with established human leukocyte antigen mutations manifest a completely different appearance on MR spectroscopy, with increases in GABA.<sup>71</sup> This finding is unsurprising because, in narcolepsy, hypocretin is deficient; hypocretin normally has a negative feedback effect on GABA anabolism. Thus, the elevation of GABA within the medial prefrontal cortex fits into the pathophysiology of narcolepsy.

### **Migraines**

Bigal et al<sup>72</sup> were the first to look at GABA concentrations in migraines by using MR spectroscopy. There was no difference between those with migraines and controls on the basis of GABA values.<sup>72</sup> Particular to this condition and the concomitant association with neurovascular alterations, GABA changes may simply reflect the effects of altered cerebral blood flow during a migraine attack.

### **Autism Spectrum Disorders**

GABA<sub>A</sub> and GABA<sub>B</sub> receptor downregulation has been proposed as a potential pathophysiologic mechanism in autism.<sup>73,74</sup> Harada et al<sup>75</sup> recently reported the first MR spectroscopy evaluation of GABA in children with autism, which demonstrated significantly reduced GABA concentration in the frontal lobes and in the GABA/Glu ratio, suggesting that GABAergic activity declines while glutamatergic activity is excessive. These reductions in GABA could explain the cognitive impairment and increased seizure risk inherent in autism.

### **Olfactory and Gustatory Disorders**

Like the other conditions described herein, the empiric effectiveness of GABA-active medications suggested the role of GABA downregulation in the case of phantogeusia and phantosmia.<sup>76</sup> In a study of patients with either condition, GABA levels were decreased within the cingulate, right and left insula, and left amygdala.<sup>77</sup> GABA agonist therapy (haloperidol or thioridazine) significantly increased these depressed GABA levels.<sup>77</sup> From this clinical research, cortical hyperactivity potentially manifests itself as spurious perceived smells and/or tastes.

### **Treatment Effects on GABA Concentration**

MR spectroscopy is emerging as a useful instrument to improve our understanding of the pharmacology and development of medications.<sup>65</sup> As a noninvasive repeatable study, MR spectroscopy could be easily used to longitudinally follow the changes in brain chemistry. Unexpected changes in brain metabolism could serve as indicators of potential neurologic complications before actual clinical findings appear.

### **GABA Agonists**

Several medications are known to act either directly on GABA receptors or the related benzodiazepine receptors. Zolpidem, used in the treatment of insomnia and acting on the GABA<sub>A</sub>R, decreased GABA levels in the thalamus but not the anterior cingulate cortex; this effect correlated with subjective nausea and dizziness.<sup>78</sup> Clonazepam also reduced GABA levels, particularly within the occipital cortex.<sup>55</sup>

## **Anti-Epileptic Drugs**

### **Management of Seizure Disorders Relies on the Preventive Function of AEDs.**

Vigabatrin acts by inhibiting GABA-T irreversibly, thereby increasing the amount of GABA available. Early studies showed a significant GABA increase, beginning within 2 hours<sup>79,80</sup> and verified by others.<sup>81,82</sup> Increased CSF and MR spectroscopy-measured GABA by vigabatrin are associated with improved seizure control<sup>83</sup>; those with lower baseline levels and steeper increases appear to respond better clinically.<sup>84</sup>

Topiramate is an AED with an imprecise mechanism of action that is thought to enhance GABA<sub>A</sub> activity. Topiramate can increase MR spectroscopy-detected GABA by 72% or 0.9 mmol/L in as little as 3–4 hours as well as its precursor, glutamine.<sup>85–88</sup>

Lamotrigine, of the newer generation of AEDs, has proved very useful in other conditions such as bipolar disorder. Despite its efficacy in seizure prevention,<sup>89</sup> MR spectroscopy showed no GABA effect for lamotrigine acutely but revealed significant GABA increases of one-quarter at 1 month.<sup>90</sup>

Gabapentin is, instead, thought to act via voltage-gated calcium channels. MR spectroscopy illustrates the GABAergic activity of gabapentin, with acute and chronic elevations in GABA<sup>90</sup> and a median concentration increase of 1.3 mmol/L within the occipital cortex within 1 hour of administration.<sup>91</sup> Levetiracetam is another AED with a tenuous mechanism of action that is thought to bind synaptic vesicles. In patients with epilepsy who responded to levetiracetam, GABA/Cr increased; this change suggests a GABAergic component that facilitates seizure prevention.<sup>5</sup>

### **Antidepressants**

SSRIs have become the mainstay of the management of mood disorders and related conditions. Given the reduction in GABA seen in depressed patients and the clinical efficacy of SSRIs, it is unsurprising that recent studies suggest that SSRIs increase GABA. A pilot study of several SSRIs showed significantly increased occipital cortex GABA (34%) after an average of 2 months of treatment.<sup>92</sup> Citalopram administration yields a 35% relative increase in GABA in the occipital cortex of healthy volunteers, confirming these findings and suggesting a pro-GABAergic effect of SSRIs.<sup>93</sup>

### **Nonpharmacologic Therapy**

Because other treatment options may have an effect on the brain chemistry of patients, it is important to systematically assess potential changes in GABA with alternative therapies. Yoga therapy for healthy volunteers yielded demonstrable increases in thalamic GABA on MR spectroscopy over a walking group,<sup>94</sup> with a significant decrease in anxiety.<sup>94</sup> On the other hand, GABA MR spectroscopy may not detect changes with some therapies: Cognitive behavioral therapy was of no benefit in increasing GABA levels in individuals with depression in 1 study.<sup>95</sup>

### **Future Directions**

MR spectroscopy has already made demonstrable advances in the noninvasive detection of differences in GABA concentrations in a variety of conditions from autism to epilepsy to

stiff-person syndrome. In addition, MR spectroscopy informs clinicians of the effects of medications on the chemical composition of the brain. The future of MR spectroscopy looks promising with the advent of advanced techniques that can better isolate individual compounds. Many limitations still exist, however: MR spectroscopy studies are lengthy and uncomfortable for patients, and MR spectroscopy of GABA requires a high degree of technical sophistication. Most pressingly, pervasive gaps in our understanding of neurochemical changes, particularly affecting GABA, persist. Another limitation in the field of MR spectroscopy results from the static approach to metabolic disruptions in the brain. With the use of other MR spectra such as carbon 13 MR spectroscopy, it is plausible that metabolite pool kinetics could be visualized, though several barriers to this approach invented in the 1990s still exist as discussed by others.<sup>96,97</sup> Future examinations by using MR spectroscopy could take advantage of these novel techniques to examine disruptions of brain chemistry in disease conditions and analyze the effectiveness and action of pharmaceuticals.

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