Published in final edited form as:

Neurology. 2008 May 27; 70(22): 2078–2080. doi:10.1212/01.wnl.0000313376.07248.28.

OCCIPITAL LEVELS OF GABA ARE RELATED TO SEVERE HEADACHES IN MIGRAINE

M.E. Bigal, MD, PhD, H. Hetherington, PhD, J. Pan, MD, PhD, A. Tsang, B. Grosberg, MD, N. Avdievich, PhD, B. Friedman, MD, and R.B. Lipton, MD

Departments of Neurology (M.E.B., R.B.L.), Epidemiology and Population Health (R.B.L.), and Emergency Medicine (B.F.), Albert Einstein College of Medicine, Bronx, NY; Montefiore Headache Center (M.E.B., A.T., B.G., R.B.L.), Bronx, NY; New England Center for Headache (M.E.B.), Stamford, CT; Department of Neurology (H.H., J.P., N.A.), Yale University School of Medicine, New Haven, CT; and Merck Research Laboratories (M.E.B.), White-house Station, NJ

Although GABA has figured prominently in theories of migraine pathogenesis,¹ brain levels of this transmitter have not been directly measured in migraineurs. This is of importance since, in migraine, neurophysiologic events account for brain hyperexcitability and subcortical disinhibition.^{2,3} Magnetic resonance spectroscopy (MRS) measures levels of metabolites in the human brain and may map regional changes in their levels.⁴ Accordingly, herein we used MRS to measure the levels of GABA in individuals with migraine with aura (MA), migraine without aura (MO), and in controls.

Methods

Individuals with MA (n = 9), MO (n = 10), and controls without headache (n = 9) were enrolled. Participants could not use migraine preventive drugs or any other on a daily basis. Subjects prospectively collected their headache information over 1 month, using a daily headache calendar. Disability was assessed with the Migraine Disability Assessment Questionnaire (MIDAS).

Migraineurs were imaged no less than 72 hours after their last headache attack. Data were acquired at 4T using a MRS INOVA system. Details of the methods are described elsewhere.⁵ Briefly, a volume of $3 \times 3 \times 1.5 \text{ cm}^3$ was used positioned within the midline of the occipital lobe using inversion recovery gradient echo images. Two 8.5-minutes acquisition were averaged to generate a final GABA spectrum, referenced to creatine (Cr) and to *N*-acetylaspartate (NAA).

We conducted cross-sectional analysis examining occipital GABA levels by headache status. We also evaluated the relationship between GABA levels and variables prospectively obtained from headache diaries (e.g., severe headaches). We powered our study based on assumptions for the GABA levels, as published previously.⁶ We had an 80% power to detect 15% change in the GABA levels in a two-sided *t* test. This study was approved by the Committee for Clinical Investigation.

Results

Most participants were women (84.7%), with a mean age of 34.5 years. Controls (mean age = 26.5, 95% CI = 22.4–30.5) were significantly younger than individuals with MO (mean = 41.4, 95% CI = 30.5–52.2). The mean age of individuals with MA was not significantly different from the other groups (34.1, 95% CI = 27.9–40.2). Age correlated with mean GABA concentration (Pearson correlation coefficient = 0.66). Individuals with MA had aura in an overall 58.3% of the attacks.

Tables 1 and 2 display the GABA concentration (millimoles per liter), GABA/Cr ratio, and total GABA (millimoles), across the different groups. The differences were not significant. For GABA, the mean values were 0.61 mmol (95% CI = 0.49–0.75) in controls, 0.67 mmol (95% CI = 0.56–0.78) in the MO group, and 0.74 mmol (95% CI = 0.58–0.89) in the MA group. Nonsignificant differences were found in the other variables as well.

Pooling the MO and MA subjects, GABA concentration was lower in individuals with severe headaches in the previous month. In those with no severe headaches, it was 0.72 ± 17 mmol/L vs 0.52 ± 0.64 mmol/L in those with one or more ($p = 0.03$). It was also lower in individuals with headaches of at least moderate severity. Finally, migraineurs with impairment (MIDAS grades II to IV) had lower GABA concentrations compared to those with no impairment (0.50 ± 0.48 mmol/L vs 0.73 ± 15 mmol/L, $p < 0.05$). After scaling by the creatine and NAA content, the findings were similar. For example, GABA/Cr ratio was also significantly lower in those with severe headaches in the past month (0.056 ± 0.08 mmol/L vs 0.068 ± 0.017 mmol/L, $p = 0.04$).

Discussion

We found that the levels of GABA are not significantly different in migraineurs and controls, or in migraine with or without aura. Accordingly, our findings do not support GABA as an important neurotransmitter initiating migraine attacks. Second, we found no difference in the interictal levels of GABA in subjects with MA and MO. If CSD is of greater importance in MA than MO, dysfunction on other neurotransmitter pathways (e.g., glutamate/AMPA–kainate) or ionic abnormalities (e.g., related to Ca, Na, Mg) may be better related with the onset of CSD.^{2,3} Finally, GABA did vary significantly as a function of severe headache attacks and of attack-related disability. Accordingly, we suggest that GABA plays a role in suppressing headache attacks. Inversely, low GABA levels may happen as a consequence of severe migraine attacks.

Cautions are required when interpreting our data. First, because MRS is a costly method, our sample size is small, although we were powered to test our a priori hypotheses. Second, GABA was measured in single voxel areas of the occipital cortex, being subject to spatial sampling error. Third, the occipital cortex was selected because it is the most frequent site of CSD and for technical reasons.⁷ It is possible that differences might be identified in other brain regions.

Acknowledgments

Disclosure: This study was sponsored by the American Headache Society (2005 Preventive Research Award) and by an unrestricted grant from Pfizer Inc. Dr. Bigal is currently a full-time employee of Merck Research Laboratories.

References

1. Welch KM, Chabi E, Bartosh K, Achar VS, Meyer JS. Cerebrospinal fluid gamma aminobutyric acid levels in migraine. *BMJ*. 1975; 3:516–517. [PubMed: 1164613]
2. Goadsby PJ. New directions in migraine research. *J Clin Neurosci*. 2002; 9:368–373. [PubMed: 12217664]
3. Moskowitz MA, Macfarlane R. Neurovascular and molecular mechanisms in migraine headaches. *Cerebrovasc Brain Metab Rev*. 1993; 5:159–177. [PubMed: 8217498]
4. Pan JW, Twieg DB, Hetherington HP. Quantitative spectroscopic imaging of the human brain at 4.1, magnetic resonance in medicine. *Magn Reson Med*. 1998; 40:363–369. [PubMed: 9727938]
5. Avdievich NI, Hetherington HP. 4T actively detunable transmit/receive transverse electromagnetic coil and 4-channel receive-only phased array for (1)H human brain studies. *Magn Reson Med*. 2004; 52:1459–1464. [PubMed: 15562466]
6. Kuzniecky R, Ho S, Pan J, et al. Modulation of cerebral GABA by topiramate, lamotrigine, and gabapentin in healthy adults. *Neurology*. 2002; 58:368–372. [PubMed: 11839834]
7. Hetherington HP, Newcomer BR, Pan JW. Measurements of human cerebral GABA at 4.1 T using numerically optimized editing pulses. *Magn Reson Med*. 1998; 39:6–10. [PubMed: 9438430]

Table 1

Measurements of GABA, as assessed by MRI spectroscopy, according to headache status

	Control	Migraine without aura	Migraine with aura	Significance
GABA concentration, mmol/L				
Mean (SD)	0.61 (0.142)	0.67 (0.15)	0.74 (0.19)	NS
95% CI	0.49–0.75	0.56–0.78	0.58–0.89	
GABA/Cr				
Mean (SD)	0.058 (0.013)	0.062 (0.014)	0.069 (0.018)	NS
95% CI	0.046–0.070	0.052–0.073	0.054–0.083	

NS = not significant.

Table 2Measurements of GABA, as assessed by MRI spectroscopy, according to headache severity^{*}

	GABA concentration, mmol/L	GABA/creatinine
Days of severe headache in past month		
None	0.72 ± 0.17	0.068 ± 0.017
1 or more	0.52 ± 0.64	0.056 ± 0.08
Significance	<i>p</i> = 0.03	<i>p</i> = 0.04
Days of headache of at least moderate intensity in past month		
<3	0.72 ± 0.10	0.075 ± 0.017
3+	0.62 ± 0.14	0.060 ± 0.012
Significance	<i>p</i> = 0.05	<i>p</i> = 0.046
Days of headache of any intensity in past month		
<6	0.69 ± 0.44	0.068 ± 0.017
6+	0.66 ± 0.50	0.056 ± 0.008
Significance	<i>p</i> = 0.6868	<i>p</i> = 0.67
Attack-related impairment	0.73 ± 15	0.76 ± 13
Little or no disability (MIDAS I)	0.50 ± 48	0.56 ± 43
At least some disability (MIDAS II–IV)	<i>p</i> < 0.05	<i>p</i> < 0.05

^{*} In individuals with migraine with or without aura.