The Journal of Headache and Pain

RESEARCH

Open Access

Gamma-aminobutyric acid and glutamate/glutamine levels in the dentate nucleus and periaqueductal gray in new daily persistent headache: a magnetic resonance spectroscopy study

Tong Chen[1,2,3], Xiaoyan Bai[1,2,3], Wei Wang[4], Xue Zhang[1,2,3], Xun Pei[1,2,3], Xueyan Zhang[5], Ziyu Yuan[4], Yuanbin Zhao[1,2,3], Qi Yang[6], Yonggang Wang[4*] and Binbin Sui[1,3*]

Abstract

Background Magnetic resonance spectroscopy (MRS) studies have indicated that the imbalance between gamma-aminobutyric acid (GABA) and glutamate/glutamine (Glx) levels was the potential cause of migraine development. However, the changes in the GABA and Glx levels in patients with New daily persistent headache (NDPH) remain unclear. This study aimed to investigate the changes in GABA and Glx levels in the periaqueductal gray (PAG) and dentate nucleus (DN) in patients with NDPH using the MEGA-PRESS sequence.

Methods Twenty-one NDPH patients and 22 age- and sex-matched healthy controls (HCs) were included and underwent a 3.0T MRI examination, using the MEGA-PRESS sequence to analyze GABA and Glx levels of PAG and DN. The correlations between these neurotransmitter levels and clinical characteristics were also analyzed.

Results There were no significant differences in the GABA+/Water, GABA+/Cr, Glx/Water, and Glx/Cr levels in both PAG and DN between the two groups (all $p > 0.05$). Moderate-severe NDPH patients had lower levels of Glx/Water ($p = 0.034$) and Glx/Cr ($p = 0.012$) in DN than minimal-mild NDPH patients. In patients with NDPH, higher Glx/Water levels in the PAG (r=-0.471, $p = 0.031$, $n = 21$) and DN (r=-0.501, $p = 0.021$, $n = 21$) and higher Glx/Cr levels in DN (r=-0.483, $p = 0.026$, $n = 21$) were found to be correlated with lower Visual Analogue Scale scores. Additionally, a positive correlation was observed between the GABA+/Cr levels in the DN and the Generalized Anxiety Disorder-7 scores ($r = 0.519$, $p = 0.039$, $n = 16$).

Conclusions The results of this study indicated that the GABA and Glx levels in the PAG and DN may not be the primary contributor to the development of NDPH. The correlations between certain clinical scales and the neurotransmitter levels may be derived from the NDPH related symptoms.

*Correspondence:
Yonggang Wang
w100yg@gmail.com
Binbin Sui
reneesui@163.com

Full list of author information is available at the end of the article

Keywords New daily persistent headache, Magnetic resonance spectroscopy, Gamma-aminobutyric acid, Glutamate/glutamine, Dentate nucleus, Periaqueductal gray

Introduction

New daily persistent headache (NDPH) is a rare primary headache with a prevalence of about 0.03-0.1% in the general population [1]. The primary characteristic of NDPH is the persistent headache that continues in a daily pattern at least three months from its onset and patients can clearly remember the exact time of the onset [2]. The headache phenotype of NDPH may resemble chronic migraine (CM) or chronic tension-type headache [3]. Severe instances may even precipitate psychiatric disorders. However, the pathogenesis of NDPH is still poorly understood [1, 4].

Previous studies have indicated neurotransmitter changes in certain regions of the brain in patients with migraine [5–7]. An imbalance between inhibitory and excitatory neurotransmitters may contribute to migraine development [8]. Magnetic resonance spectroscopy (MRS) offers a non-invasive method to quantify metabolites. In particular, the MEGA-PRESS sequence enables quantification of the concentration of gamma-aminobutyric acid (GABA) and glutamate/glutamine (Glx) [9]. The MEGA-PRESS sequence uses J-difference editing to resolve overlapping signals, enabling the accurate quantitative detection of modified GABA and Glx levels [9]. This technology has been widely applied in the study of GABA and Glx in the brain of diverse populations, including healthy people [10], Alzheimer's disease [11], Parkinson's disease [12], and migraine [6–8]. MEGA-PRESS sequence might be one of the most reliable and commonly used methods for measuring GABA.

Periaqueductal gray (PAG) is one of the most important central hubs for processing ascending and descending pain signals [13]. It has extensive connections with the cortex, various brainstem nuclei, and cerebellum [14–16]. Numerous studies have reported abnormalities in PAG and cerebellum in CM and NDPH [17–20]. A prior study revealed that patients with CM exhibited significantly decreased levels of GABA in the dentate nucleus (DN) and notably elevated levels of Glx in PAG compared to healthy controls (HCs). A strong correlation between these neurochemical levels and migraine characteristics was also identified [6]. It remains unknown whether there are any alterations in GABA and Glx levels of the PAG and DN in patients with NDPH. The investigation in these areas may help to understand the underlying pathological mechanisms of NDPH.

Therefore, the aim of this study was to quantify the GABA and Glx levels in the DN and PAG of NDPH patients using the MEGA-PRESS sequence and to investigate the correlation between GABA and Glx levels and clinical characteristics of patients with NDPH. We hypothesized that GABA-GLX imbalance exists in the PAG and DN of patients with NDPH.

Methods

Participants

Twenty-six patients with NDPH were prospectively recruited from the Headache Centre of the Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, from January 2021 to July 2022. All NDPH patients were diagnosed by two experienced headache physicians according to the diagnostic criteria of the International Classification of Headache Disorders, Third version (ICD-3) [2]; Inclusion criteria: (1) no other neurological or psychiatric disorders; (2) no claustrophobia and other contraindications to MRI examination; (3) no history of cranial and cerebral surgeries or trauma. Exclusion criteria: (1) obvious infarct lesions in the brain; (2) poor cooperation and the quality of MRI images could not satisfy the subsequent analysis; (3) incomplete data.

Thirty-three age- and sex-matched HCs were enrolled in this study. The inclusion criteria for the HC group were as follows: (1) no history of any headache; (2) no history of neurological or psychiatric disorders; (3) no claustrophobia and other contraindications to MRI examination; (4) the quality of the MRI images could satisfy the subsequent analysis. The subjects were excluded if they had obvious infarct lesions, poor MRI image quality, and incomplete data.

Demographic and general clinical information such as age, gender, body mass index (BMI), age of onset of disease, and disease duration were recorded for all participants. Multiple clinical scales have been used to assess the clinical characteristics of NDPH patients. Visual analog scale (VAS) scores were used to assess the headache intensity; the Headache Impact Test-6 (HIT-6) [21] was used to assess the impact of headache in daily life; the Pittsburgh Sleepiness Quality Index (PSQI) [22] was used to assess the quality of sleep; the Generalized Anxiety Disorder-7 (GAD-7) [23] was used to assess anxiety and the Patient Health Questionnaire-9 (PHQ-9) [24] was used to assess depression. We also performed a subgroup analysis of patients with NDPH based on the headache intensity. NDPH patients were divided into minimal-mild group (VAS score 0–3) and moderate-severe group (VAS score 4–10).

This study was a sub-study of the ongoing Chinese Headache Disorders Registry Study (CHAIRS, trial registration: NCT05334927). All participants signed an informed consent form, and the Ethics Committee of

Beijing Tiantan Hospital reviewed and approved the study (KY-2022-044).

MRI images acquisition and processing

All participants were examined on a 3.0T MR scanner (Signa Premier, GE Healthcare, USA) equipped to use a 48-channel head coil. All participants had their heads immobilized with foam pads and were asked to keep their heads as still as possible.

3D T_1 MP-RAGE sequence was performed to obtain structural data using the following parameters: sagittal acquisition, echo time (TE)=3 ms, repetition time (TR)=7.2 ms, with 1-mm isotropic resolution, field of view (FOV)=256 mm; acquisition matrix=256; slice number=192; flip angle=8°; preparation time=880 ms; recovery time=400 ms; acceleration factor=2; (acquisition time=4 min). The scanning parameters for the MEGA-PRESS sequence were as follows: TE=68 ms, TR=2000 ms, number of points=2048; spectral width=2000 Hz; and number of averages=160 (acquisition time=11 min 28 s). Six very selective saturation (VSS) pulses were used to minimize errors in chemical-shift displacement and to achieve consistent localization volumes across measurements [25]. According to previous literature, two 20×20×20 mm^3 voxels were placed in PAG and DN, respectively (Fig. 1). All images acquired from the MEGA-PRESS sequence were processed using GANNET 3.1 (http://gabamrs.org) [26] (Fig. 2). A Gaussian baseline model was used to fit the edited GABA signal and a Lorentz-Gaussian line shape was employed to fit the unsuppressed water signal. The processing steps included the following: a combination of phased array coil data, time-domain frequency, phase correction using spectral correction, and application of an exponential apodization function for line broadening. Subsequent steps involved fast Fourier transform, time averaging, and frequency and phase correction based on fitting the water and creatine (Cr) signals. Finally, data were pairwise rejected if the fitting parameters deviated by more than three standard deviations from the mean, and subtraction was used to generate the edited difference spectrum and to extract the OFF spectrum. All MRS spectra were

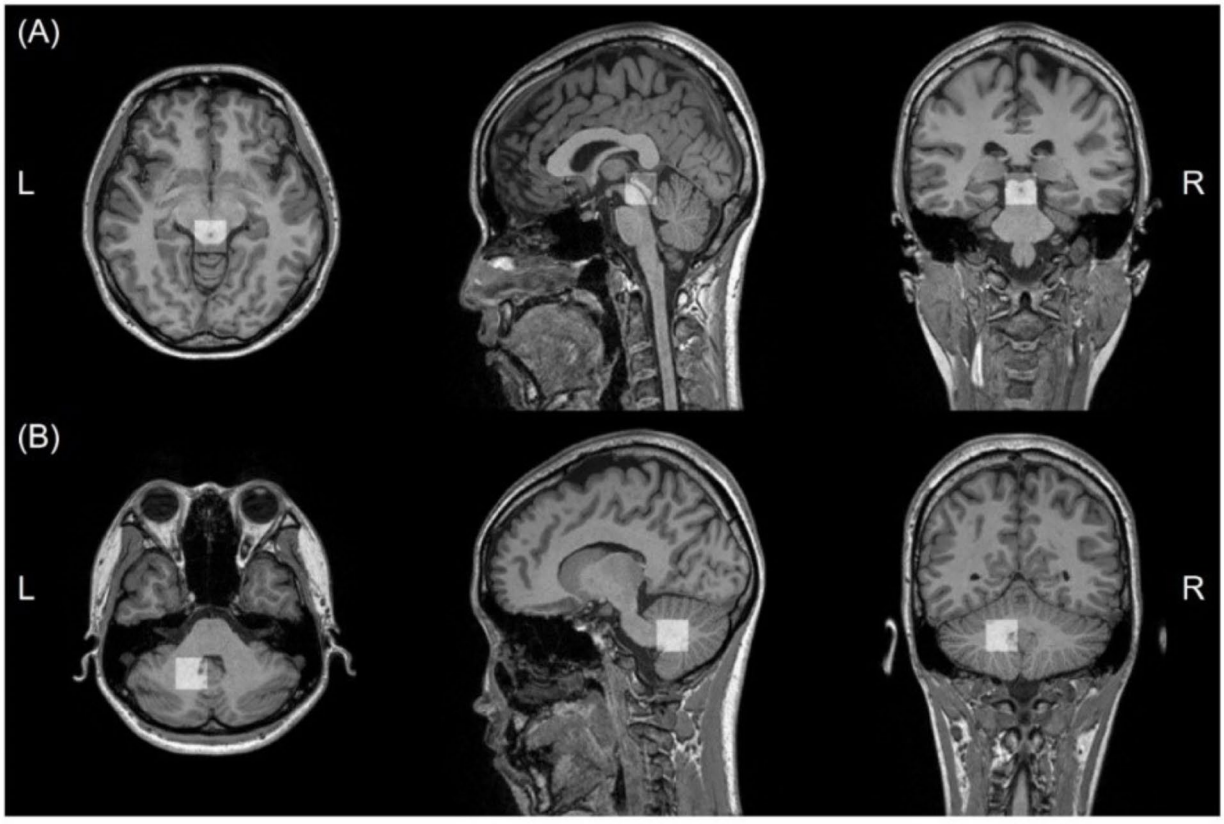

Fig. 1 The examples of voxel placements in the PAG (**A**) and DN (**B**). PAG, periaqueductal gray; DN, dentate nucleus; L, Left; R, Right

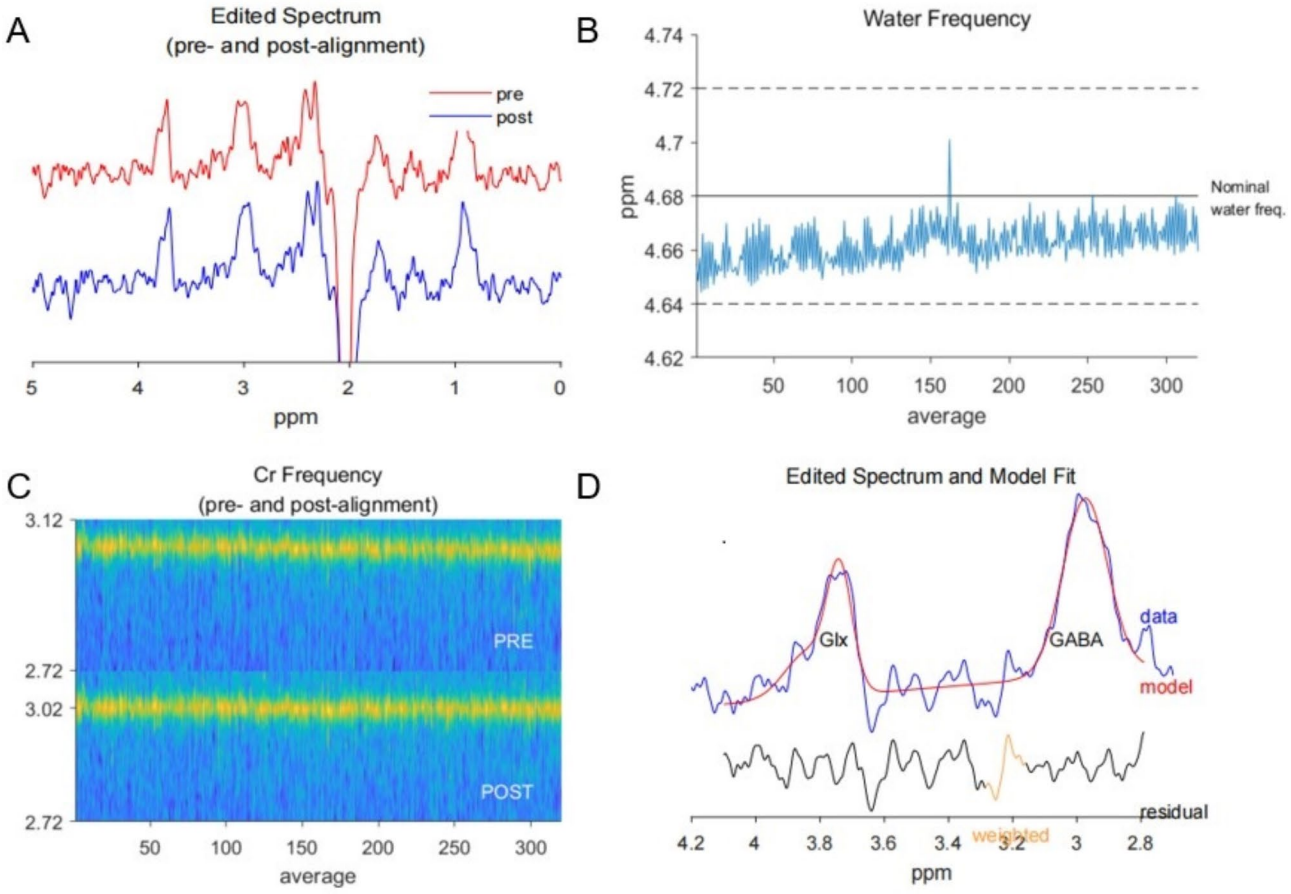

Fig. 2 MEGA-PRESS data processing. (**A**) The processed gamma-aminobutyric acid (GABA)-edited difference spectrum before frequency and phase correction (red) and after (blue). (**B**) The frequency of the maximum point in the residual water signal is plotted against time. (**C**) The y-axis represents the frequency (in ppm) of the Cr signal, before frequency-and-phase correction and after. (**D**) The GABA-edited spectrum is shown in blue. The model of best fit is shown in red. The residual between these two is shown in black. GABA, gamma-aminobutyric acid; Glx, glutamate/glutamine; Cr, creatine

reviewed by two experts to exclude data with significant motion artifacts as well as insufficient water suppression.

Statistical analysis

The sample size was calculated according to the neurotransmitter levels in the previous study [6]. We set the target power (1-β) at 0.80 and the α-error at 0.05. We calculated that at least 19 participants were needed for each group. All statistical analyses were performed using SPSS software (version 25.0, IBM, Armonk, NY, USA). All data were checked for normality using the Shapiro-Wilk test. Quantitative data that fit the normal distribution were expressed using mean ± standard deviation, and that did not fit the normal distribution were expressed using median and quartiles. Categorical variables were expressed using frequencies and percentages. Differences in sex composition between groups were assessed using the chi-squared test. The independent samples t-test and the Mann-Whitney-U test were applied for comparisons of the two groups, based on whether the quantitative data conformed to a normal distribution. Pearson's or Spearman's correlation was used to analyze the correlation between neurotransmitter levels and clinical characteristics. $p<0.05$ were considered statistically significant.

Results

Demographics and clinical characteristics

In total, twenty-six NDPH patients and 33 HCs were recruited, five NDPH patients and 9 HCs were excluded due to incomplete images, and two HCs were excluded due to poor image quality. Finally, twenty-one NDPH patients and 22 HCs were included.

There were no significant differences in age, gender, and BMI between the NDPH and HC groups. Sixteen NDPH patients completed the HIT-6, PSQI, GAD-7, and PHQ-9 scale assessments. All demographic and clinical characteristics are presented in Table 1.

Neurotransmitter levels in NDPH and HC groups

In the PAG, there were no significant differences in GABA+/Water levels, GABA+/Cr levels, Glx/Water, and Glx/Cr between NDPH and HC groups (all $p>0.05$).

Table 1 Demographic and clinical data

	HC($n=22$)	NDPH($n=21$)	*p*-Value
Age (years)	29.00 (27.00-45.25)	38.00 (17.00-60.50)	0.780
Male, n (%)	11 (50.00)	13 (61.90)	0.432
BMI (kg/m^2)	22.14 ± 3.09	21.96 ± 3.67	0.870
Disease duration (years)	NA	3.00 (1.00-11.50)	NA
Age of onset (years)	NA	31.00 (13.50–44.00)	NA
VAS scores	NA	4.00 (3.00–7.00)	NA
HIT-6 (36–78)	NA	64.69 ± 8.61 ($n=16$)	NA
PHQ-9 (0–27)	NA	10.69 ± 6.28 ($n=16$)	NA
GAD-7 (0–21)	NA	6.94 ± 4.64 ($n=16$)	NA
PSQI (0–21)	NA	10.25 ± 4.45 ($n=16$)	NA

NDPH, New Daily Persistent Headache; HC, Healthy control; BMI, Body Mass Index; VAS, Visual analog scale, HIT-6, Headache Impact Test-6; PHQ-9, Patient Health Questionnaire-9; GAD-7, Generalized Anxiety Disorder-7; PSQI, Pittsburgh Sleep Quality Index

Table 2 MRS data in periaqueductal gray and dentate nucleus

	HC($n=22$)	NDPH($n=21$)	*p*-Value
Periaqueductal gray			
GABA+/Water (i.u.)	2.00 ± 0.47	2.01 ± 0.61	0.952
GABA+/Cr	0.20 ± 0.04	0.19 ± 0.05	0.559
Glx/Water (i.u.)	4.50 ± 1.22	4.75 ± 0.92	0.459
Glx/Cr	0.12 ± 0.04	0.12 ± 0.02	0.804
Dentate nucleus			
GABA+/Water (i.u.)	2.80 ± 0.54	2.74 ± 0.57	0.728
GABA+/Cr	0.20 ± 0.04	0.19 ± 0.05	0.755
Glx/Water (i.u.)	5.73 ± 1.37	5.43 ± 1.39	0.476
Glx/Cr	0.11 ± 0.03	0.10 ± 0.03	0.304

NDPH, New Daily Persistent Headache; HC, Healthy control; GABA, gamma-aminobutyric acid; Glx, glutamate/glutamine; Cr, creatine; i.u., institutional unit

In the DN, no significant differences were found in GABA+/Water levels, GABA+/Cr levels, Glx/Water, and Glx/Cr between NDPH and HC groups (all $p>0.05$). More detailed MRS data were shown in Table 2; Fig. 3.

Subgroup analysis of neurotransmitter levels in NDPH

Nine patients were divided into the minimal-mild group and 12 patients were divided into the moderate-severe group. In the DN, the Glx/Water ($p=0.034$) and Glx/Cr ($p=0.012$) levels in the moderate-severe group were significantly lower than the minimal-mild group. However, no significant differences were found in the GABA+/Water ($p=0.650$) and GABA+/Cr ($p=0.499$) levels. No significant differences were found in the neurotransmitter levels in PAG between the minimal-mild and moderate-severe groups (all $p>0.05$). The details were shown in Table 3.

Correlation between neurotransmitter levels and clinical characteristics

The Glx/Water levels in the PAG (r=-0.471, $p=0.031$, $n=21$) and DN (r=-0.501, $p=0.021$, $n=21$) and the Glx/Cr levels in DN (r=-0.483, $p=0.026$, $n=21$) were observed to be negatively correlated with the VAS scores (Fig. 4A-C). The GABA+/Cr levels in the DN were positively correlated with the GAD-7 scores ($r=0.519$, $p=0.039$, $n=16$) (Fig. 4D).

Discussion

In this study, we investigated the GABA and Glx levels within the PAG and DN of NDPH patients using the MEGA-PRESS sequence. We found that there were no significant differences in these neurotransmitter levels between HC and NDPH groups. In the DN, subgroup analysis showed that moderate-severe NDPH patients had lower Glx concentrations than minimal-mild patients. Furthermore, there were significant correlations between neurotransmitter levels and VAS scores, as well as the GAD-7 scores of NDPH patients.

Several MRI studies have revealed abnormal alterations in the structure, functional connectivity, and cerebral blood flow of the cerebellum in patients with migraine [27–29]. As the largest nucleus of the cerebellum, DN may play an important role in the pathogenesis of migraine. The role of PAG in migraine has also been emphasized by many studies [29–31]. Both DN and PAG have glutamatergic neurons and GABAergic neurons [32–34]. Several studies reported abnormal GABA-Glx imbalance in migraine [5, 8]. The previous MEGA-PRESS study in CM patients has demonstrated the GABA-Glx imbalance in PAG and DN [6]. Therefore, these two regions were selected as ROIs in this study. The GABA and Glx levels were measured in DN and PAG in NDPH patients for the first time. Interestingly, we did not observe abnormal alterations in the levels of these neurotransmitters in either the PAG or DN in patients with NDPH compared with HCs.

Although several factors have been proposed associated with NDPH, such as infections (e.g., viral or bacterial infections) and cervical spine joint hyperactivity [35–37], the underlying mechanism of NDPH remains unclear. So far, MRI studies on NDPH were not common and the results vary widely. Negative results were reported in white matter abnormalities [38], voxel-based morphometry (VBM) structural brain alterations [39], as well as glymphatic dysfunction [40]; while some studies have identified abnormalities in structure, cerebral perfusion, white matter micro-structural changes, and functional connectivity in patients with NDPH [20, 41–45]. The findings of our study provide the first group of data in neurotransmitter levels changes in NDPH cases, which indicated that the pathogenesis of NDPH might differ

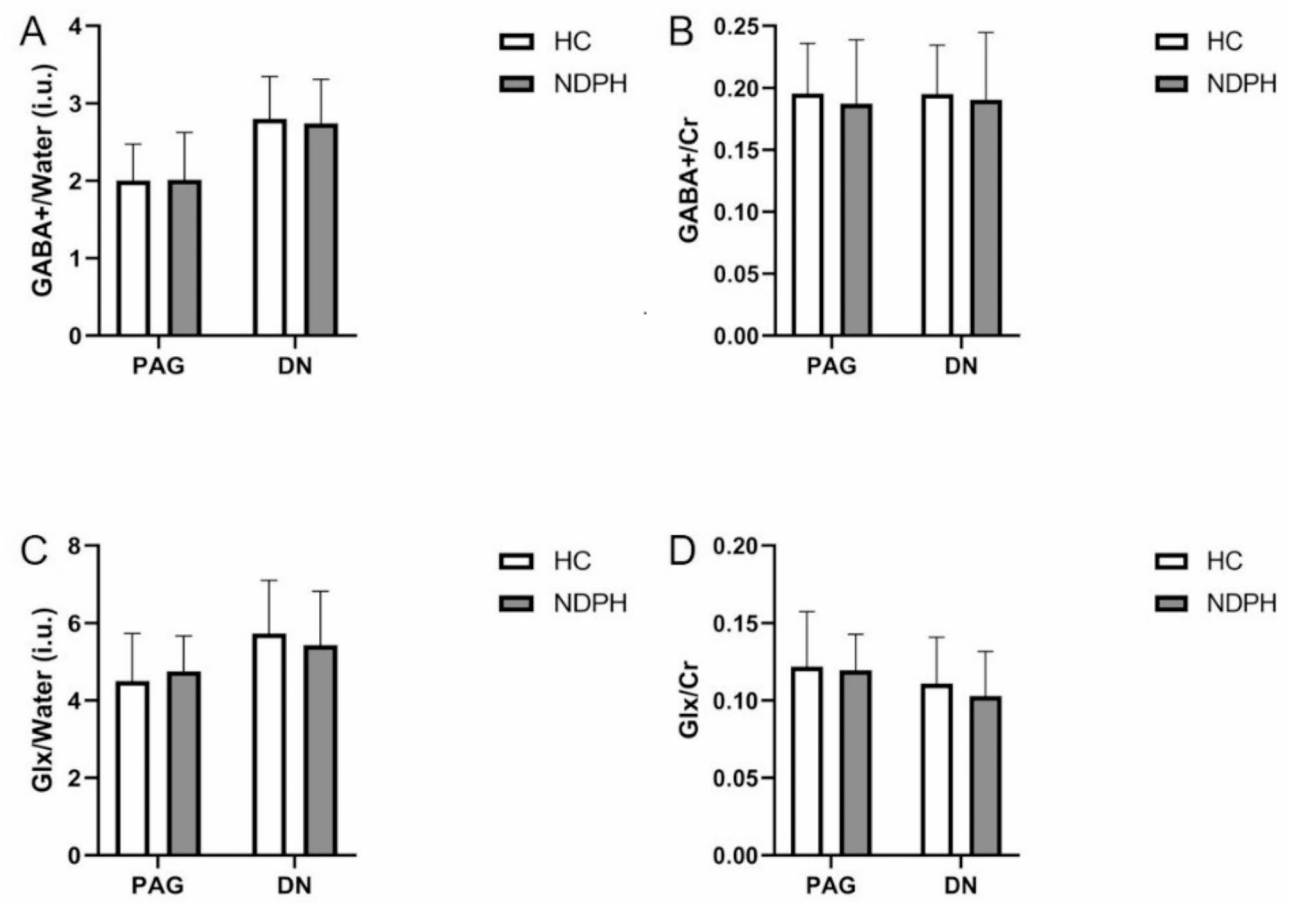

Fig. 3 Comparisons of neurotransmitter levels between NDPH and HC groups. (**A**) GABA+/Water (i.u.) in the PAG and DN of the HC and NDPH groups. (**B**) GABA+/Cr in the PAG and DN of the HC and NDPH groups. (**C**) Glx/Water (i.u.) in the PAG and DN of the HC and NDPH groups. (**D**) Glx/Cr in the PAG and DN of the HC and NDPH groups. PAG, periaqueductal gray; DN, dentate nucleus; HC, healthy control; NDPH, new daily persistent headache; GABA, gamma-aminobutyric acid; Glx, glutamate/glutamine; Cr, creatine; i.u., institutional unit

Table 3 Subgroup analysis of neurotransmitter levels in NDPH

	Minimal-mild ($n=9$)	Moderate-severe ($n=12$)	*p*-Value
Periaqueductal gray			
GABA+/Water (i.u.)	1.99 ± 0.64	2.03 ± 0.62	0.874
GABA+/Cr	0.18 ± 0.06	0.19 ± 0.04	0.596
Glx/Water (i.u.)	5.20 ± 0.84	4.42 ± 0.85	0.052
Glx/Cr	0.13 ± 0.03	0.11 ± 0.02	0.229
Dentate nucleus			
GABA+/Water (i.u.)	2.81 ± 0.73	2.69 ± 0.45	0.650
GABA+/Cr	0.20 ± 0.07	0.18 ± 0.03	0.499
Glx/Water (i.u.)	6.11 ± 1.39	4.91 ± 1.21	**0.034**
Glx/Cr	0.12 ± 0.03	0.09 ± 0.03	**0.012**

GABA, gamma-aminobutyric acid; Glx, glutamate/glutamine; Cr, creatine; i.u., institutional unit

from that of CM, and it is not primarily caused by an imbalance of GABA-GLX in PAG and DN.

The factors that affect the GABA and Glx levels were complex. The findings of MRS studies on migraine have also been heterogeneous in recent years. The location of ROI placement [46], the stimulation [47], the presence or absence of an aura [48], and the severity of migraine [49, 50] may all have an impact on the results. The headache intensity in NDPH patients was comparatively milder than that in the previous study [39]. Whether it is one of the reasons for the negative results in the current study may need further validation. NDPH patients were categorized into a self-limiting form and a persistent refractory form [2]. In another recent study, NDPH patients were classified into three subtypes using cluster analysis [39]. The heterogeneity of patients with NDPH may also be an important reason for the negative results.

In addition to GABA and Glx, other neurotransmitters such as serotonin may also contribute to the development of migraine [51, 52]. It has been suggested that there may be interactions between serotonin, GABA, and Glx [53–55]. Taking selective serotonin reuptake inhibitors has been linked to increased GABA levels in the occipital lobe [53, 54]. Animal studies have demonstrated that sumatriptan also inhibits GABAergic and glutamatergic synaptic transmission within the PAG [56]. PAG also has

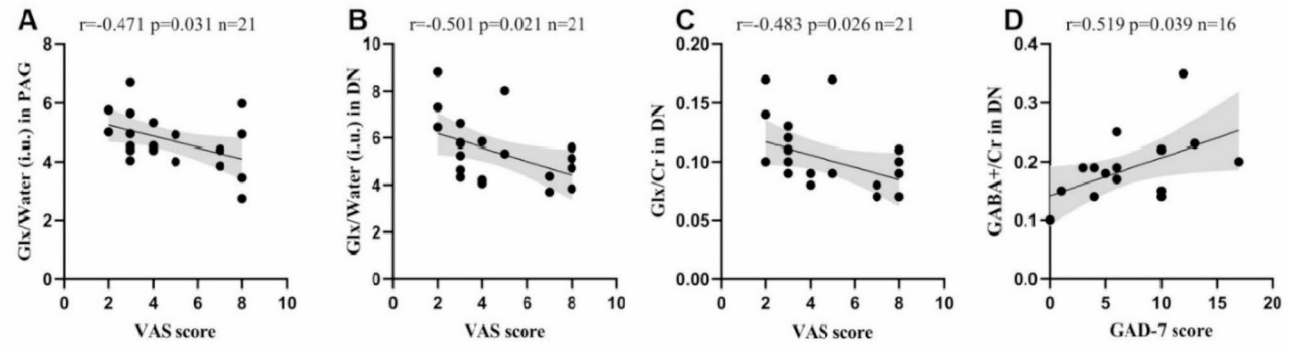

Fig. 4 Correlation between clinical characteristics and neurotransmitter levels. (**A**) Negative correlation between Glx/Water in the PAG and the VAS score (r=-0.471, p=0.031, n=21). (**B**) Negative correlation between Glx/Water in the DN and the VAS score (r=-0.501, p=0.021, n=21). (**C**) Negative correlation between Glx/Cr in the DN and the VAS score (r=-0.483, p=0.026, n=21). (**D**) Positive correlation between GABA+/Water in the DN and the GAD-7 score (r=0.519, p=0.039, n=16). Gray shading represents the 95% confidence intervals of the partial correlations. PAG, periaqueductal gray; DN, dentate nucleus; Cr, creatine; GABA, gamma-aminobutyric acid; Glx, glutamate/glutamine; VAS, Visual analog scale; GAD-7, Generalized Anxiety Disorder-7

somatostatin, dopamine, and other neurotransmitters [57, 58]. The role of these neurotransmitters in the pathogenesis of NDPH was not verified in this current study. It is plausible that other mechanisms beyond the known neurotransmitter interactions exist in NDPH patients.

Depression, anxiety, and sleep disturbance were prevalent comorbidities in patients with NDPH [4]. Previous studies have shown that the majority of NDPH patients exhibit high scores on both GAD-7 and PHQ-9 assessments [59]. In patients with migraine, Wang et al. [6] reported that the neurotransmitter levels may be correlated with depression, sleep, and disability severity. It has been proposed that lower GABA levels may be associated with more severe migraine [49]. In the present study, moderate-severe patients also had significantly lower Glx levels than the minimal-mild patients. In addition, our results showed that the Glx levels in DN and PAG were negatively correlated with VAS scores. The GABA level in DN was found to be positively correlated with the GAD-7 score. This phenomenon may be associated with neurotransmitter adaptation to clinical characteristics. In the previous study, Peek et al. [60] also found that the increased GABA levels in the anterior cingulate cortex may be a protective factor to suppress further migraine attacks. Alterations in GABA and Glx levels may be adaptive responses to disease states. The relationship between neurotransmitters and migraine characteristics is complex and not yet fully understood. Further research is needed to investigate the mechanisms associated with migraine characteristics and neurotransmitter levels.

There were some limitations in our study. First, this study was a single-center cross-sectional study with a relatively small sample size. Considering the incidence of NDPH, the results of our study might provide data to help with the understanding of this rare disease. Another limitation of our study was that the clinical scales of the NDPH patients were not complete, which might affect the correlation results. There are still some difficulties in achieving high-quality MRS acquisition in the PAG due to its small size. In this study, we used an ROI size of $20\times20\times20mm^3$ to achieve this purpose, which was larger than PAG. Our previous study on patients with migraine found abnormalities in neurotransmitter levels in PAG using the same protocol, which may indicate the feasibility and reliability of the MEGA-PRESS protocol in this area [6]. This approach improved the signal-to-noise ratio, but sacrificed the regional specificity in a certain degree. Recently, Sirucek L et al. [25] proposed a new approach to achieve higher-quality MRS acquisition in PAG. The new imaging method would help to obtain high-quality MRS data with better regional specificity to investigate the neurotransmitter levels in the PAG in future studies. Furthermore, due to the relatively long acquisition time, only DN and PAG were chosen and included in the analysis. Whether there are any changes in the neurotransmitter levels of other regions of the brain still needs further investigation. A longitudinal study with larger sample size and complete clinical scale data will be needed for validation of the findings in the current study.

Conclusion

In conclusion, the results of this study indicated that the neurotransmitter levels changes in the periaqueductal gray and dentate nucleus may not be the primary contributor to the development of NDPH, which may be taken as supportive data for the different underlying mechanisms between NDPH and primary migraine diseases. Further studies using multimodal MRI are necessary and may provide more valuable information for the exploration of underlying pathological mechanisms in patients with NDPH.

Acknowledgements
We would like to express our gratitude to all participants and physicians at the Headache Center, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University in this study. We appreciate the support of the General Electric Company.

Author contributions
TC, YGW, and BBS supported the conception and design of this project. WW, XYB, XZ, XYZ, ZYY, XP, QY, and YBZ acquired data. TC and XYB analyzed the data. XYB and WW contributed to data quality control. TC produced the first draft. All authors contributed intellectual content to the revised manuscript and have read and approved the final manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (Grant No. 62271061, 32170752, 91849104, and 31770800), Beijing Municipal Natural Science Foundation (L232130), and the National Natural Science Foundation of Beijing (Z200024).

Data availability
Data can be made available upon request.

Declarations

Ethics approval and consent to participate
This study had been registry on Clinical Trial (NCT05334927). All participants signed an informed consent form, and the Ethics Committee of Beijing Tiantan Hospital reviewed and approved the study (KY-2022-044).

Consent for publication
All authors have agreed to the current submission.

Competing interests
The authors declare no competing interests.

Author details
[1]Tiantan Neuroimaging Center of Excellence, China National Clinical Research Center for Neurological Diseases, No.119 South Fourth Ring West Road, Fengtai District, Beijing 100070, China
[2]Department of Radiology, Beijing Tiantan Hospital, Capital Medical University, No.119 South Fourth Ring West Road, Fengtai District, Beijing 100070, China
[3]Department of Neuroradiology, Beijing Neurosurgical Institute, Capital Medical University, Beijing, China
[4]Headache Center, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, No.119 South Fourth Ring West Road, Fengtai District, Beijing 100070, China
[5]Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
[6]Department of Radiology, Beijing Chaoyang Hospital, Key Lab of Medical Engineering for Cardiovascular Disease, Capital Medical University, Ministry of Education, Beijing, China

Received: 6 July 2024 / Accepted: 17 August 2024
Published online: 29 August 2024

References

1. Yamani N, Olesen J (2019) New daily persistent headache: a systematic review on an enigmatic disorder. J Headache Pain 20:80. https://doi.org/10.1186/s10194-019-1022-z
2. (2018) Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 38:1–211. https://doi.org/10.1177/0333102417738202
3. Gelfand AA, Robbins MS, Szperka CL (2022) New Daily Persistent Headache—A Start with an Uncertain End. JAMA Neurol 79:733. https://doi.org/10.1001/jamaneurol.2022.1727
4. Cheema S, Mehta D, Ray JC et al (2023) New daily persistent headache: a systematic review and meta-analysis. Cephalalgia 43:033310242311680. https://doi.org/10.1177/03331024231168089
5. Peek AL, Leaver AM, Foster S et al (2021) Increased GABA + in people with migraine, Headache, and Pain Conditions- A potential marker of Pain. J Pain 22:1631–1645. https://doi.org/10.1016/j.jpain.2021.06.005
6. Wang W, Zhang X, Bai X et al (2022) Gamma-aminobutyric acid and glutamate/glutamine levels in the dentate nucleus and periaqueductal gray with episodic and chronic migraine: a proton magnetic resonance spectroscopy study. J Headache Pain 23:83. https://doi.org/10.1186/s10194-022-01452-6
7. Zhang X, Wang W, Bai X et al (2023) Changes in gamma-aminobutyric acid and glutamate/glutamine levels in the right thalamus of patients with episodic and chronic migraine: a proton magnetic resonance spectroscopy study. Headache 63:104–113. https://doi.org/10.1111/head.14449
8. Bathel A, Schweizer L, Stude P et al (2018) Increased thalamic glutamate/glutamine levels in migraineurs. J Headache Pain 19:55. https://doi.org/10.1186/s10194-018-0885-8
9. Mullins PG, McGonigle DJ, O'Gorman RL et al (2014) Current practice in the use of MEGA-PRESS spectroscopy for the detection of GABA. NeuroImage 86:43–52. https://doi.org/10.1016/j.neuroimage.2012.12.004
10. Grewal M, Dabas A, Saharan S et al (2016) GABA quantitation using MEGA-PRESS: Regional and hemispheric differences: Regional and Hemispheric GABA levels. J Magn Reson Imaging 44:1619–1623. https://doi.org/10.1002/jmri.25324
11. Bai X, Edden RAE, Gao F et al (2015) Decreased γ-aminobutyric acid levels in the parietal region of patients with Alzheimer's disease: in vivo GABA levels measurement in AD. J Magn Reson Imaging 41:1326–1331. https://doi.org/10.1002/jmri.24665
12. Gong T, Xiang Y, Saleh MG et al (2018) Inhibitory motor dysfunction in parkinson's disease subtypes. Magn Reson Imaging 47:1610–1615. https://doi.org/10.1002/jmri.25865
13. Zhang H, Zhu Z, Ma W-X et al (2024) The contribution of periaqueductal gray in the regulation of physiological and pathological behaviors. Front NeuroSci 18:1380171. https://doi.org/10.3389/fnins.2024.1380171
14. Sillery E, Bittar RG, Robson MD et al (2005) Connectivity of the human periventricular-periaqueductal gray region. J Neurosurg 103:1030–1034. https://doi.org/10.3171/jns.2005.103.6.1030
15. Cao J, Zhang Y, Li H et al (2021) Different modulation effects of 1 hz and 20 hz transcutaneous auricular vagus nerve stimulation on the functional connectivity of the periaqueductal gray in patients with migraine. J Transl Med 19:354. https://doi.org/10.1186/s12967-021-03024-9
16. Bagley EE, Ingram SL (2020) Endogenous opioid peptides in the descending pain modulatory circuit. Neuropharmacology 173:108131. https://doi.org/10.1016/j.neuropharm.2020.108131
17. Kros L, Angueyra Aristizábal CA, Khodakhah K (2018) Cerebellar involvement in migraine. Cephalalgia 38:1782–1791. https://doi.org/10.1177/0333102417752120
18. Domínguez C, López A, Ramos-Cabrer P et al (2019) Iron deposition in periaqueductal gray matter as a potential biomarker for chronic migraine. Neurology 92. https://doi.org/10.1212/WNL.0000000000007047
19. Wang W, Qiu D, Mei Y et al (2024) Altered functional connectivity of brainstem nuclei in new daily persistent headache: evidence from resting-state functional magnetic resonance imaging. CNS Neurosci Ther 30:e14686. https://doi.org/10.1111/cns.14686
20. Szabo E, Chang YC, Shulman J et al (2022) Alterations in the structure and function of the brain in adolescents with new daily persistent headache: a pilot MRI study. Headache 62:858–869. https://doi.org/10.1111/head.14360
21. Kosinski M, Bayliss MS, Bjorner JB et al A six-item short-form survey for measuring headache impact: The HIT-6ä
22. Buysse DJ, Reynolds CF, Monk TH et al (1989) The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193–213. https://doi.org/10.1016/0165-1781(89)90047-4
23. Spitzer RL, Kroenke K, Williams JBW, Löwe B (2006) A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 166:1092. https://doi.org/10.1001/archinte.166.10.1092
24. Kroenke K, Spitzer RL, Williams JBW (2001) The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 16:606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x
25. Sirucek L, Zoelch N, Schweinhardt P (2024) Improving magnetic resonance spectroscopy in the brainstem periaqueductal gray using spectral registration. Magn Reson Med 91:28–38. https://doi.org/10.1002/mrm.29832
26. Edden RAE, Puts NAJ, Harris AD et al (2014) Gannet: a batch-processing tool for the quantitative analysis of gamma-aminobutyric acid–edited MR spectroscopy spectra. Magn Reson Imaging 40:1445–1452. https://doi.org/10.1002/jmri.24478

27. Fu T, Liu L, Huang X et al (2022) Cerebral blood flow alterations in migraine patients with and without aura: an arterial spin labeling study. J Headache Pain 23:131. https://doi.org/10.1186/s10194-022-01501-0
28. Affatato O, Rukh G, Schiöth HB, Mwinyi J (2023) Volumetric differences in Cerebellum and Brainstem in patients with migraine: a UK Biobank Study. Biomedicines 11:2528. https://doi.org/10.3390/biomedicines11092528
29. Mehnert J, May A (2019) Functional and structural alterations in the migraine cerebellum. J Cereb Blood Flow Metab 39:730–739. https://doi.org/10.1177/0271678X17722109
30. Chen Z, Chen X, Liu M et al (2017) Disrupted functional connectivity of periaqueductal gray subregions in episodic migraine. J Headache Pain 18:36. https://doi.org/10.1186/s10194-017-0747-9
31. Messina R, Sudre CH, Wei DY et al (2023) Biomarkers of Migraine and Cluster Headache: differences and similarities. Ann Neurol 93:729–742. https://doi.org/10.1002/ana.26583
32. Bagnall MW, Zingg B, Sakatos A et al (2009) Glycinergic projection neurons of the Cerebellum. J Neurosci 29:10104–10110. https://doi.org/10.1523/JNEUROSCI.2087-09.2009
33. Xie L, Wu H, Chen Q et al (2023) Divergent modulation of pain and anxiety by GABAergic neurons in the ventrolateral periaqueductal gray and dorsal raphe. Neuropsychopharmacol 48:1509–1519. https://doi.org/10.1038/s41386-022-01520-0
34. Ma W, Li L, Kong L et al (2023) Whole-brain monosynaptic inputs to lateral periaqueductal gray glutamatergic neurons in mice. CNS Neurosci Ther cns 14338. https://doi.org/10.1111/cns.14338
35. Diaz-Mitoma F, Vanast WJ, Tyrrell DLJ (1987) Increased frequency of epstein-barr virus excretion in patients with new daily persistent headaches. Lancet 329:411–415. https://doi.org/10.1016/S0140-6736(87)90119-X
36. Santoni JR, Santoni-Williams CJ (1993) Headache and painful lymph-adenopathy in Extracranial or systemic infection: etiology of New Daily Persistant headaches. Intern Med 32:530–532. https://doi.org/10.2169/internalmedicine.32.530
37. Rozen T, Roth J, Denenberg N (2006) Cervical spine joint hypermobility: a possible predisposing factor for New Daily Persistent Headache. Cephalalgia 26:1182–1185. https://doi.org/10.1111/j.1468-2982.2006.01187.x
38. Rozen TD (2016) New daily persistent headache: a lack of an association with white matter abnormalities on neuroimaging. Cephalalgia 36:987–992. https://doi.org/10.1177/0333102415612766
39. Naegel S, Zeller J, Hougaard A et al (2022) No structural brain alterations in new daily persistent headache – a cross sectional VBM/SBM study. Cephalalgia 42:335–344. https://doi.org/10.1177/03331024211045653
40. Zhang X, Wang W, Zhang X et al (2023) Normal glymphatic system function in patients with new daily persistent headache using diffusion tensor image analysis along the perivascular space. Headache 63:663–671. https://doi.org/10.1111/head.14514
41. Mei Y, Wang W, Qiu D et al (2023) Micro-structural white matter abnormalities in new daily persistent headache: a DTI study using TBSS analysis. J Headache Pain 24:80. https://doi.org/10.1186/s10194-023-01620-2
42. Zhang X, Wang W, Bai X et al (2023) Alterations in regional homogeneity and multiple frequency amplitudes of low-frequency fluctuation in patients with new daily persistent headache: a resting-state functional magnetic resonance imaging study. J Headache Pain 24:14. https://doi.org/10.1186/s10194-023-01543-y
43. Qiu D, Wang W, Mei Y et al (2023) Brain structure and cortical activity changes of new daily persistent headache: multimodal evidence from MEG/sMRI. J Headache Pain 24:45. https://doi.org/10.1186/s10194-023-01581-6
44. Wang W, Yuan Z, Zhang X et al (2023) Mapping the aberrant brain functional connectivity in new daily persistent headache: a resting-state functional magnetic resonance imaging study. J Headache Pain 24:46. https://doi.org/10.1186/s10194-023-01577-2
45. Bai X, Wang W, Zhang X et al (2022) Cerebral perfusion variance in new daily persistent headache and chronic migraine: an arterial spin-labeled MR imaging study. J Headache Pain 23:156. https://doi.org/10.1186/s10194-022-01532-7
46. De La González J, Ramos A, Mato-Abad V et al (2013) Higher glutamate to glutamine ratios in Occipital regions in Women with Migraine during the Interictal State. Headache 53:365–375. https://doi.org/10.1111/head.12030
47. Siniatchkin M, Sendacki M, Moeller F et al (2012) Abnormal changes of synaptic excitability in migraine with aura. Cereb Cortex 22:2207–2216. https://doi.org/10.1093/cercor/bhr248
48. Zielman R, Wijnen JP, Webb A et al (2017) Cortical glutamate in migraine. Brain 140:1859–1871. https://doi.org/10.1093/brain/awx130
49. Bigal ME, Hetherington H, Pan J et al (2008) Occipital levels of GABA are related to severe headaches in migraine. Neurology 70:2078–2080. https://doi.org/10.1212/01.wnl.0000313376.07248.28
50. Stærmose TG, Knudsen MK, Kasch H, Blicher JU (2019) Cortical GABA in migraine with aura -an ultrashort echo magnetic resonance spectroscopy study. J Headache Pain 20:110. https://doi.org/10.1186/s10194-019-1059-z
51. Hamel E, Currents H (2007) Serotonin and migraine: Biology and Clinical implications. Cephalalgia 27:1293–1300. https://doi.org/10.1111/j.1468-2982.2007.01476.x
52. Razeghi Jahromi S, Togha M, Ghorbani Z et al (2019) The association between dietary tryptophan intake and migraine. Neurol Sci 40:2349–2355. https://doi.org/10.1007/s10072-019-03984-3
53. Sanacora G, Mason GF, Rothman DL, Krystal JH (2002) Increased occipital cortex GABA concentrations in depressed patients after Therapy with selective serotonin reuptake inhibitors. AJP 159:663–665. https://doi.org/10.1176/appi.ajp.159.4.663
54. Bhagwagar Z, Wylezinska M, Taylor M et al (2004) Increased brain GABA concentrations following Acute Administration of a selective serotonin reuptake inhibitor. AJP 161:368–370. https://doi.org/10.1176/appi.ajp.161.2.368
55. Jacobs GE, Der Grond JV, Teeuwisse WM et al (2010) Hypothalamic glutamate levels following serotonergic stimulation: a pilot study using 7-Tesla magnetic resonance spectroscopy in healthy volunteers. Prog Neuropsychopharmacol Biol Psychiatry 34:486–491. https://doi.org/10.1016/j.pnpbp.2010.01.019
56. Jeong H-J, Chenu D, Johnson EE et al (2008) Sumatriptan inhibits synaptic transmission in the Rat Midbrain Periaqueductal Grey. Mol Pain 4. https://doi.org/10.1186/1744-8069-4-54. 1744-8069-4–54
57. Taylor NE, Pei J, Zhang J et al (2019) The role of glutamatergic and dopaminergic neurons in the Periaqueductal Gray/Dorsal raphe: separating analgesia and anxiety. https://doi.org/10.1523/ENEURO.0018-18.2019. eNeuro 6:ENEURO.0018-18.2019
58. Zhang Y, Huang X, Xin W-J et al (2023) Somatostatin neurons from Periaqueductal Gray to Medulla Facilitate Neuropathic Pain in male mice. J Pain 24:1020–1029. https://doi.org/10.1016/j.jpain.2023.01.002
59. Uniyal R, Paliwal VK, Tripathi A (2017) Psychiatric comorbidity in new daily persistent headache: a cross-sectional study. Eur J Pain 21:1031–1038. https://doi.org/10.1002/ejp.1000
60. Peek AL, Leaver AM, Foster S et al (2021) Increase in ACC GABA + levels correlate with decrease in migraine frequency, intensity and disability over time. J Headache Pain 22:150. https://doi.org/10.1186/s10194-021-01352-1

Publisher's note