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A 'complex' of brain metabolites distinguish altered chemistry in the cingulate cortex of episodic migraine patients

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ABSTRACT

Despite the prevalence of migraine, the pathophysiology of the disease remains unclear. Current understanding of migraine has alluded to the possibility of a hyperexcitable brain. The aim of the current study is to investigate human brain metabolite differences in the anterior cingulate cortex (ACC) during the interictal phase in migraine patients. We hypothesized that there may be differences in levels of excitatory neurotransmitters and/or their derivatives in the migraine cohort in support of the theory of hyperexcitability in migraine. 2D *J*-resolved proton magnetic resonance spectroscopy (^{1}H-MRS) data were acquired on a 3 Tesla (3 T) MRI from a voxel placed over the ACC of 32 migraine patients (MP; 23 females, 9 males, age 33 ± 9.6 years) and 33 healthy controls (HC; 25 females, 8 males, age 32 ± 9.6 years). Amplitude correlation matrices were constructed for each subject to evaluate metabolite discriminability. ProFit-estimated metabolite peak areas were normalized to a water reference signal to assess subject differences. The initial analysis of variance (ANOVA) was performed to test for group differences for all metabolites/creatine (Cre) ratios between healthy controls and migraineurs but showed no statistically significant differences. In addition, we used a multivariate approach to distinguish migraineurs from healthy subjects based on the metabolite/Cre ratio. A quadratic discriminant analysis (QDA) model was used to identify 3 metabolite ratios sufficient to minimize minimum classification error (MCE). The 3 selected metabolite ratios were aspartate (Asp)/Cre, *N*-acetyl aspartate (NAA)/Cre, and glutamine (Gln)/Cre. These findings are in support of a 'complex' of metabolite alterations, which may underlie changes in neuronal chemistry in the migraine brain. Furthermore, the parallel changes in the three-metabolite 'complex' may confer more subtle but biological processes that are ongoing. The data also support the current theory that the migraine brain is hyperexcitable even in the interictal state.

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1. Introduction

Although the cause of migraine attacks remains unknown, a number of studies have indicated that migraine alters brain structure and function, including behavioral studies (Borsook et al., 2014; Brigo et al., 2013; Hoffken et al., 2009) and neuroimaging studies (Sprenger and Borsook, 2012). An increasing number of studies have evaluated measures of brain chemistry in migraine patients (see below). Altered chemistry in migraine may provide a basis for the purported cortical hyperexcitability (Coppola et al., 2007; Demarquay et al., 2013), and could be a target for evaluating treatment efficacy in responders and non-responders, as has been reported in other chronic pain conditions such as fibromyalgia (Harris et al., 2013), or evaluation of the effects of treatments (e.g., topiramate) on brain metabolites (Moore and Wardrop, 2006).

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MRS studies of migraine have recently been reviewed elsewhere (Reyngoudt et al., 2012). These studies have consistently suggested altered energy metabolism (Reyngoudt et al., 2011) in migraine patients but few studies have reported alterations in glutamate (Glu) or gamma aminobutyric acid (GABA) in migraine patients, the latter two components providing a potential basis for hyperexcitability (either increased Glu or decreased GABA or some combination that contributes to potential neuronal hyperexcitability). A recent paper reported significantly increased GABA in migraine using a Mescher-Garwood point-resolved spectroscopy (MEGA-PRESS) sequence (Aguila et al., 2015) and higher glutamine (Gln)/glycine (Gly) ratios in women than in men during their interictal phase of migraine (Gonzalez de la Aleja et al., 2013), offering some support for the hyperexcitability thesis. The hyperexcitability thesis relates to the sensitization that results from cortical spreading depression (CSD). CSD has been implicated in the pathogenesis of migraine but is still not fully understood. Studies have indicated that the wave of activation and subsequent inhibition caused by CSD results in the sensitization of the trigeminal vascular system and its central projections (Cutrer and Charles, 2008). Others have suggested that hyperexcitability of the trigeminovascular neurons may stem from altered descending modulation of the brain stem which may cause a loss of inhibition or enhanced facilitation (Moulton et al., 2008). MRS studies have found evidence of this with increases in both excitatory (Gonzalez de la Aleja et al,. 2013) and inhibitory (Aguila et al., 2015) neurotransmitters suggesting a potentially more complex changes in brain neurochemistry that contributes to a hyperexcitable state.

Here we have used an approach to optimize the measurements of both GABA and Glu with a 2D *J*-resolved approach, focusing on the anterior cingulate cortex (ACC). We have chosen the ACC because of its putative role in multiple processing in migraine including involvement in salience (Borsook et al., 2013), descending modulation (Mainero et al., 2011), and altered resting state connectivity (Russo et al., 2012; Tessitore et al., 2015; Xue et al., 2013). Conventional proton MRS (^{1}H-MRS) is often hampered by low spectral resolution and metabolite peak overlap, especially to measure GABA and Gln/Glu concentrations. Reliable detection and quantization of metabolite concentrations is thus problematic. Two-dimensional (2D) ^{1}H-MRS methodologies effectively increase spectral resolution by spreading metabolite resonances over a 2D surface and accounting for *J*-coupling resonances. We hypothesized that we would be able to determine measures of GABA and/or Glu in migraine and healthy subjects and that differences between two populations can be differentiated based on the chemical signature as has been done in other pain states (Foerster et al., 2012; Niddam et al., 2011) as well as acute pain (Cleve et al., 2015). We have previously shown that metabolites can differentiate healthy subjects from migraine patients using a linear discriminate analysis (LDA) approach (Prescot et al., 2009). Here in a larger patient population along with a QDA analysis we hope to gain a more thorough understanding of how metabolite concentrations (specifically GABA and Glu) differ and if the differences are in support of the current theory of a hyperexcitable migraine brain (Welch et al., 1990).

2. Methods

2.1. Subject selection

The local Institutional Review Board (IRB) of Partners Health Care approved the present study protocol, which met the requirements for investigations in human subjects. A total of 33 healthy control (HC; 25 females, 8 males, mean age = 32 ± 9.6 years) subjects and 32 migraine patients (MP; 23 females, 9 males, mean age = 33 + 9.6 years) were included in this study. All subjects were between the ages of 18–50, right-handed, non-smokers, and had no significant history of other chronic pain, psychiatric, neurological or any other major disorders. At the beginning of each study visit, subjects were screened for depression (Beck Depression Inventory II (Beck et al., 1996), exclusionary score > 25 [moderate to severe depression]) as well as a urine test for barbiturates, benzodiazepines, amphetamine, cocaine, tetrahydrocannabinol, phencyclidine and opioids (excluding prescription pain medications). Healthy controls were also excluded if they were on any prescription medications or had any history of migraine. All migraine subjects fit the criteria for episodic migraine in accordance with the International Classification for Headache II and confirmed by a neurologist. The migraine subjects also had to have had a history of migraine for at least 3 years and were excluded if they were on any daily preventative medications for their migraine. In order to confirm the migraine subjects were in the interictal phase, we asked if they had an attack within 24 h leading to their study visit and then followed up with them 72 h after the study visit. If subjects experienced an attack within that window of time, they were disqualified.

2.2. 2D MRS data acquisition

All MR imaging and 2D *J*-resolved ^{1}H MRS measurements were performed using a 3 Tesla Siemens (Erlangen, Germany) TIM Trio™ whole-body MRI system housed at McLean Hospital (Belmont, MA). Radiofrequency (RF) excitation and signal reception was achieved using a manufacturer-supplied circularly polarized body RF coil and a 12-channel phased array receive-only RF coil (operated in the four-cluster mode, 3 elements per cluster), respectively. Subjects were positioned supine and foam pads were utilized to fixate the head within the RF receive coil. Following the acquisition of low-resolution localizer MR images, high-resolution 3D magnetization-prepared rapid gradient echo (MP-RAGE; TR/TE/TI = 2000/3.53/1100 ms; FOV = 256 × 256 × 224 mm; isotropic 1 mm in-plane resolution) MRI data then were acquired to facilitate accurate MRS voxel positioning and for post hoc within-voxel tissue-type segmentation. All spectroscopy data were acquired from a voxel ($30 \times 22 \times 25$ mm^3) positioned within the anterior cingulate cortex (ACC), which was obliqued along the sagittal plane and positioned to cover predominantly gray matter. B0 shimming was performed over the MRS voxel using the manufacturer-supplied phase map method as well as additional interactive manual shimming until a full-width at half-maximum (FWHM) of ≤12 Hz was observed for the real component of the unsuppressed water signal line width. 2D *J*-resolved ^{1}H MRS data were recorded using a modified PRESS sequence as described in an earlier report (Prescot and Renshaw, 2013). Briefly, 2D MRS acquisition parameters were as follows: TR/TE = 2000/31–229 ms; ΔTE = 2 ms; 4 signal averages per TE step; 2D spectral width = 2000 × 500 Hz; 2D matrix size = 2048 × 100 Hz; maximum echo sampling based on the echo center of the first echo (i.e. TE = 31 ms); total acquisition time = 28 min 18 s. Outer-volume suppression and solvent water suppression were achieved using manufacturer-supplied techniques as described elsewhere (Prescot and Renshaw, 2013). Water unsuppressed 2D ^{1}H MRS data also were recorded from the ACC voxel using 2 signal averages per TE step. The RF transmitter frequency was set relative to total ACC (3.0 ppm) and tissue water (4.7 ppm) resonances for the water suppressed and unsuppressed measurements, respectively.

2.3. Tissue segmentation

The BET (Smith, 2002) and FAST (Zhang et al., 2001) tools provided with the freely-available FMRIB Software Library (FSL) (Smith et al., 2004) were used to perform skull stripping and whole brain tissue segmentation, respectively. For each subject dataset, home-written MATLAB (version 2010b, The MathWorks, Natick, MA) functions then were used to extract the obliqued ACC MRS voxel to obtain within-voxel gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) tissue content for each subject. The GM percentage was calculated as the ration to total brain matter (i.e. 100 × GM / [WM + GM]).

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