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Alterations of GABA and glutamate–glutamine levels in premenstrual dysphoric disorder: A 3T proton magnetic resonance spectroscopy study

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ABSTRACT

Increasing evidence has suggested that the GABAergic neurotransmitter system is involved in the pathogenesis of premenstrual dysphoric disorder (PMDD). We used proton magnetic resonance spectroscopy (^{1}H MRS) to investigate whether PMDD is associated with alterations in brain GABA levels. Levels of glutamate–glutamine (Glx) were also explored. Participants comprised 22 women with PMDD and 22 age-matched healthy controls who underwent 3 T ^{1}H MRS during the late luteal phase of the menstrual cycle. GABA+ and Glx levels were quantified in the anterior cingulate cortex/medial prefrontal cortex (ACC/mPFC) and the left basal ganglia (ltBG). Water-scaled GABA+ concentrations and GABA+/tCr ratios were significantly lower in both the ACC/mPFC and ltBG regions of PMDD women than in healthy controls. Glx/tCr ratios were significantly higher in the ACC/mPFC region of PMDD women than healthy controls. Our preliminary findings provide the first report of abnormal levels of GABA+ and Glx in mood-related brain regions of women with PMDD, indicating that dysregulation of the amino acid neurotransmitter system may be an important neurobiological mechanism in the pathogenesis of PMDD.

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1. Introduction

Premenstrual dysphoric disorder (PMDD) is a clinical syndrome which includes a range of affective and somatic symptoms that periodically occur during the late luteal phase of the menstrual cycle and remit after the onset of menses (Steiner, 2000). The classical symptoms related to mood changes include irritability, depression, dysphoria, anxiety, and affective lability. PMDD is a severe form of premenstrual syndrome (PMS) that affects only 3–9% of women (Halbreich, 2010). The underlying mechanisms of PMDD are largely unknown.

Gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in human brain (McCormick, 1989), affects various physiological functions. A number of preclinical and clinical studies have pointed to the involvement of the GABA neurotransmitter system in PMDD (Halbreich, 2003; Yonkers et al., 2008). Most studies have focused on neurosteroids, such as allopregnanolone

(ALLO) and pregnenolone, and their interactions with GABA$_A$ receptors (Bäckström et al., 2003; Amin et al., 2006; Bäckström et al., 2013). ALLO and pregnenolone, neuroactive derivatives of progesterone, have been found to be positive modulators of the GABA$_A$ receptor (Majewska et al., 1986). Neurosteroids were able to modulate the subunit composition of the GABA$_A$ receptor (Lambert et al., 2003), thus altering the function of the GABA$_A$ receptor. The paradoxical effect of ALLO mediated by the GABA$_A$ receptor may induce the negative mood symptoms in some women (Bäckström et al., 2011). Additionally, Halbreich et al. (1996) found a greater premenstrual decrease in plasma levels of GABA in women with PMDD compared with controls. Menstrual cycle-related fluctuations in neurosteroid modulation of the GABAergic system appears to be important in the pathogenesis of PMDD.

The excitatory neurotransmitter glutamate (Glu) is counterbalanced in the cortex by the inhibitory action of GABA. Magnetic resonance spectroscopy studies have suggested that glutamatergic abnormalities play an important role in the pathophysiology of major mood disorders (Salvadore and Zarate, 2010; Yuksel and Ongur, 2010). Neurosteroids also modulate the N-methyl-D-aspartate (NMDA) glutamate receptor (Baulieu, 1997), thus altering

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brain excitability. Measurement of cortical excitability using tran-scranial magnetic stimulation (TMS) demonstrated that PMDD subjects showed more facilitation than control subjects during the luteal phase (Smith et al., 2003), indicating an alteration in balance between cortical excitation and inhibition. However, research on excitatory or inhibitory neurotransmitter levels in PMDD has been limited.

In vivo proton magnetic resonance spectroscopy (^{1}H MRS) pro-vides a unique opportunity to noninvasively detect and quantify brain metabolites, including N-acetyl-aspartate (NAA), myo-inositol (mI), choline (Cho), glutamate–glutamine (Glx), total creatine (tCr) and lactate (Lac). However, measurement of GABA using conventional ^{1}H MRS is difficult due to the spectral overlap by stronger signals of other major metabolites (Govindaraju et al., 2000). An editing technique based on partially refocused J-couplings has been introduced as MEGA-PRESS by Mescher et al. to detect GABA signals (Mescher et al., 1998). This technique also allows the detection of Glx signals, due to the high structural and chemical similarities between Glx and GABA (Geramita et al., 2011). Currently, the MEGA-PRESS technique has been successfully applied in a wide variety of neuroscientific and clinical studies (Edden et al., 2009; Goto et al., 2010; Harada et al., 2011; Kakeda et al., 2011; Plante et al., 2012; Gao et al., 2013).

In the present study, the MEGA-editing technique was used to compare Glx and GABA levels between PMDD women and matched controls during the late luteal phase of the menstrual cycle. We investigated two brain regions, the anterior cingulate cortex/medial prefrontal cortex (ACC/mPFC) and the left basal ganglia (ltBG). These two regions were selected both because of their integral roles in mood disorder pathophysiology (Marchand, 2010; Price and Drevets, 2012; Stan et al., 2014) and the feasibility of obtaining MRS spectra with high quality. We hypothesized that PMDD women would have lower GABA and higher Glx levels than matched healthy controls.

2. Methods

2.1. Participants

Participants comprised 44 right-handed, regularly menstruating women (22 PMDD women and 22 age-matched healthy controls) who were recruited from the local medical school. The protocol was approved by the institutional review board, and all subjects provided written informed consent after a detailed description of the study.

The diagnosis PMDD subjects was based on DSM-IV criteria (American Psychiatry Association, 1994). Each woman was given a Structured Clinical Inter-view for DSM-IV (SCID) for Axis I disorders. A psychiatrist conducted all SCID interviews during the follicular phase. Both PMDD women and healthy controls (HCs) had no current or past personal or family history of any Axis I disorder. In addition, none of the subjects had taken prescription medication, hormonal preparation (including oral contraceptives), alcoholic beverages or cigarettes for at least 6 months before enrollment. All subjects were prospectively screened for 2 months using the Daily Record of Severity of Problems (DRSP) to record severity of mood and physical symptoms (Endicott et al., 2006). All women with PMDD had at least a 50% increase in severity of four or more mood symptoms during the late luteal phase (average score for the week before onset of menses) than during the follicular phase (average score for the week following the end of menses). According to ΔDRSP scores (difference between follicular and luteal phases), PMDD women were graded as follows: 11 for mild (25–35); 6 for moderate (35–45); 3 for severe (45–55). The most common symptoms among the PMDD group were depression, irritability, mood swings, and breast swelling.

2.2. Timing of magnetic resonance scans

Ovulation was assessed with a urinary luteinizing hormone kit (BOSON, Xiamen, China), because non-ovulation does not cause PMDD. According to individual menstrual cycle length, all scans were performed in the late luteal phase (1–7 days before onset of menses). Premenstrual symptoms appear promi-nently in this menstrual phase. All subjects reported that menses began within 6 days after scanning, which ensured data validity.

2.3. Imaging procedures

Magnetic resonance imaging (MRI) and ^{1}H MRS were carried out using a 3T scanner (Philips Achieva TX, Best, The Netherlands), equipped with an eight-channel phased-array head coil. For each subject, a T1-weighted three-dimensional TFE scan was acquired for MRS voxel placement and subsequent tissue segmenta-tion. The scanning parameters were as follows: repetition time (TR)=8.2 ms; echo time (TE)=3.7 ms; slice thickness=1 mm; matrix=256×256; field of view=24×24 cm^2; flip angle=8°. Images were reconstructed with 1×1×1 mm^3 isotropic voxel.

The volume of interest (VOI) with a size of 3×3×3 cm^3 was chosen in two regions: (1) the anterior cingulate cortex (ACC) encompassing portions of the medial prefrontal cortex (mPFC) and hence termed ACC/mPFC; (2) the left basal ganglia (ltBG), as shown in Figs. 1A–D. The medial sagittal plane was chosen as a reference slice of the VOI in the ACC/mPFC. The ACC/mPFC voxel was located with the inferior edge of the voxel parallel to the descending surface of the corpus
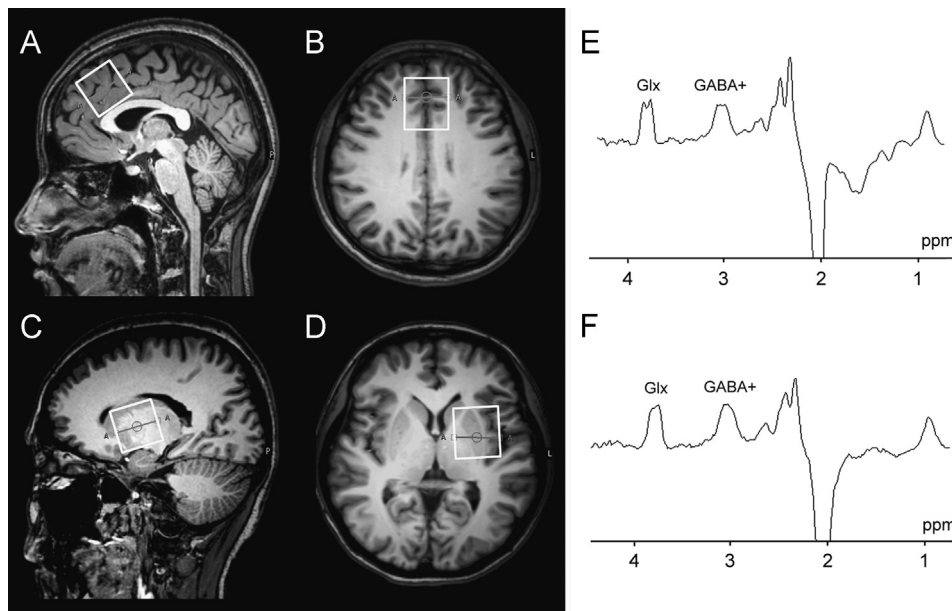
Fig. 1. Magnetic resonance spectroscopy voxel placement and resulting spectra. T1-weighted TFE images show single-voxel placements centered on the anterior cingulated cortex/median prefrontal cortex (ACC/mPFC) in the sagittal (A), axial (B) projections and on the left basal ganglia (ltBG) in the sagittal (C), axial (D) projections. Representative spectra were obtained from the ACC/mPFC (E) and the ltBG (F) using the MEGA-PRESS sequence. The combined measure of glutamine and glutamate (Glx) is resolved at 3.75 ppm., and gamma-aminobutyric acid (GABA+) is resolved at 3.01 ppm.