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Research Report

Prefrontal GABA concentration changes in women—Influence of menstrual cycle phase, hormonal contraceptive use, and correlation with premenstrual symptoms

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ABSTRACT

Prefrontal regions are involved in processing emotional stimuli and are a topic of interest in clinical and neurological research. Although sex steroids are potent neuromodulators, the influence of menstrual cycle phase and hormonal contraceptive use is rarely taken into account in neuroimaging studies. Our purpose was to evaluate changes in gamma-aminobutyric acid (GABA) in women, as measured by magnetic resonance spectroscopy (MRS), with phases of the menstrual cycle and use of hormonal contraceptives, and to assess correlations with premenstrual symptoms.Three MRI sessions per cycle were obtained in the natural cycle group, and two sessions in the hormonal contraceptives group. In addition to an anatomical scan, single voxel MRS in the prefrontal area was performed. After quality control, 10 women with natural cycle and 21 women taking hormonal contraceptives were included for analysis. Peripheral blood samples were obtained to determine endogenous hormone concentrations. Subjects were asked to complete a daily rating of severity of problems questionnaire, to quantify premenstrual symptoms. In the natural cycle group, we found a significant increase in prefrontal GABA concentration at the time of ovulation. Conversely, in the hormonal contraceptives group, no differences were found between the pill phase and pill-free phase. GABA concentrations did not significantly correlate with endogenous hormone levels, nor with premenstrual symptoms. Our results indicate that spectroscopically measured GABA concentrations are higher during ovulation in women with a natural menstrual cycle. We suggest that neuroimaging studies should take into account this variability.

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1. Introduction

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the human brain, and is therefore of interest in several subfields of clinical and neurological research (Puts and Edden, 2012; Mullins et al., 2012). Although in the human brain, it is only present in millimolar concentrations, thanks to advances in magnetic resonance techniques, it has become possible to identify endogenous concentrations of GABA, non-invasively and in-vivo, by using edited MR spectroscopy (MRS). Cortical GABA concentrations are assessed in research for several conditions such as epilepsy (Simister et al., 2003), major depressive disorder (Hasler et al., 2007; Croarkin et al., 2011), bipolar disorder (Kaufman et al., 2009), schizophrenia (Tayoshi et al., 2010), panic disorder (Hasler et al., 2009; Long et al., 2013), attention deficit hyperactivity disorder (ADHD) (Edden et al., 2012), and for brain plasticity in motor neurons (Stagg, 2013). Also, local prefrontal GABA modulations have been associated with working memory (Michels et al., 2012).

GABA concentrations have been historically assessed most commonly in the occipital regions, due to practical and technical considerations (absence of air-containing structures, more homogeneous environment, less motion artifacts). However, more recently there is increasing interest in prefrontal GABA concentrations (Hasler et al., 2007, 2009; Waddell et al., 2011; Long et al., 2013; Stan et al., 2014). This shift of attention is due to the fact that prefrontal regions are commonly associated with emotion-regulation (Yamasaki et al., 2002; Gingnell et al., 2013; Epperson, 2013), other higher order cognitive functions (Frith and Dolan, 1996), and the prefrontal cortex is of interest in several neuro-psychiatric diseases. Prior to the clinical manifestation of these disorders, there may be associated alterations or imbalances in regional neurotransmitter concentrations (Waddell et al., 2011). Prefrontal and anterior cingulate cortex (ACC) GABA levels may index the degree of negative emotions in depressive episodes (Hasler and Northoff, 2011).

Early researchers in this field suggested a potential effect of menstrual cycle phase on cortical GABA concentrations, and a possible link to clinical conditions such as premenstrual syndrome (PMS), and/or premenstrual dysphoric disorder (Epperson et al., 2002; Backstrom et al., 2003). Hormonal fluctuations of the menstrual cycle seem to have an effect on cortical GABA levels, or vice-versa. Progesterone has a binding site at the GABA-A receptor complex, modulating neural plasticity and excitability (Kaore et al., 2012). Using transcranial magnetic stimulation (TMS), excitability of the motor cortex was more inhibited during the luteal phase in a control population, as compared to PMS subjects (Smith et al., 2002); these authors pointed to a possible deficiency in GABAergic function in the PMS group. Low GABA plasma levels in the luteal phase of PMS subjects have been observed almost two decades ago (Halbreich et al., 1996). MRS results in the lentiform nucleus, frontal lobe and (non-significantly) cingulate voxels, show that GABA concentrations decrease in the luteal phase, compared to the follicular phase (Harada et al., 2011).

One other possible factor that is almost never taken into account is the use of hormonal contraceptives (HC). The synthetic progestins contained in HC may also interact with the progesterone binding site of the GABA-A receptor, changing its configuration and behavior (Stell et al., 2003). Also, women can experience PMS-like symptoms during their pill-free week (of inactive phase) (Cullberg, 1972; Rapkin et al., 2006; Rapkin and Akopians, 2012).

Despite these promising findings, uncertainties remain regarding the validity of these results. The study by Epperson et al. (2002) is overall well designed, but only considers an occipital voxel, and has a relatively large age-spread, which has been shown to affect GABA concentrations (Gao et al., 2013). Harada et al. (2011) partially confirmed the cycle-dependent GABA fluctuations, but only in a healthy subgroup without premenstrual symptoms (because these symptoms were not assessed), and their study population contained only 7 women. In order to avoid these possible cycle-dependent effects, some researchers are now advocating scanning only men (Near et al., 2014), which is also a practical confound, and always limits conclusions.

In the scientific literature there is a growing interest in measuring GABA concentrations in prefrontal areas with MRS, and in identifying differences in GABA concentrations in different anatomical regions (van der Veen and Shen, 2013). Therefore, when measuring cortical GABA concentration through edited MRS, it is important to eliminate uncertainties about the influence of menstrual cycle phase, premenstrual symptoms and hormonal contraceptive use. Our aim was to study time-dependent differences of GABA concentrations in the prefrontal region through a longitudinal study in young, healthy women. Although some literature regarding menstrual cycle related GABA changes and possible interactions with hormones and premenstrual symptoms exists, we consider this research as being exploratory, and do not propose a strong a priori hypothesis.

2. Results

2.1. Subjects

Table 1 shows an overview of the performed procedures; several subjects were excluded for further analysis, for a variety of reasons:

(1) Coincidental abnormalities in the brain on the T1 weighted images by a senior radiologist (3 subjects of the HC-group were excluded).
(2) One subject had a markedly abnormal hormonal estradiol value in the follicular phase (more than 6 standard deviations above average), and an unusually long menstrual cycle length (more than 12 standard deviations above average).
(3) Due to suboptimal quality of the edited GABA MR spectra (grades 3 and 4), 38 scans out of 170 were excluded.

Finally, because we have to exclude as many inter-subject differences as possible, we only retain data of subjects from which the spectra in *all* sessions have sufficient quality.

What remains, is a total of 76 spectra: 42 (2×21) from the hormonal contraceptives (HC) group, and 33 (3×11) from the natural cycle (NC) group. The mean age of the remaining HC group is (22.5 ± 2.6) years and (24.3 ± 3.6) years for the NC group, which means that there is no significant age difference