Alternations in the Relationships Between Cortical Amino Acids in PMDD

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Introduction
The increased interest in the possible role of GABA in depressive disorders stems from recent studies which have demonstrated significantly reduced GABA levels in patients with unipolar depression [1]. GABA is the major inhibitory neurotransmitter in the adult, mammalian brain and is synthesized in the neuron by the conversion of glutamate in the presence of GAD (glutamate decarboxylase), and the two may be functionally linked through neurotransmitter cycling and activity. In women, GABA levels systematically vary across the menstrual cycle, dropping after the follicular phase to the late-luteal phase [2]. The present study sought to determine the GABA/Glu and GABA/Gln relationship in healthy women and those diagnosed with pre-menstrual dysphoric disorder (PMDD.)

Methods
6 healthy women with no history of psychiatric disorder and 5 women meeting the DSM-IV criteria for PMDD were studied. Subjects were scanned 3 times during one complete menstrual cycle (follicular phase, mid-luteal phase, and late-luteal phase). Spectroscopic data were acquired from a 3x3x1.5 cm³ voxel in the occipital cortex. GABA was acquired using the J-editing DANTE [3] sequence (TE = 68 ms, TR = 5 s). Glutamate (Glu) and glutamine (Gln) were acquired with a spin-echo sequence (TE = 12 ms, TR = 5s) with ISIS localization. Metabolites were quantified by reference to tissue creatine (Cr = 9 mmol/g) which, in turn, was measured relative to tissue water in each subject. The proportion of tissue and the percent of grey matter in the MRS voxel was measured using automated image segmentation of quantitative T1 and B1 images [4]. Linear regression analysis were conducted on the relationship between GABA, Glu, Gln, and estradiol levels in both groups across the menstrual cycle.

Results
A significant negative, linear correlation was observed in both the PMDD subjects (p = 0.001) and the healthy controls (p = 0.001) between the GABA and glutamate concentrations over the entire menstrual cycle. However, the slope of the regression was considerably greater for the PMDD subjects than for the healthy controls (-0.174 and -0.225 respectively). There was also a significant negative correlation between the GABA and Gln concentrations both for the healthy controls (p < 0.05) and the PMDD subjects (p < 0.05). Finally, there was a significant positive correlation between estradiol levels and Glu levels for the healthy controls (p < 0.01). However, the PMDD subjects showed a trend in the opposite direction that did not reach significance. No differences in grey matter or tissue content were observed.

Discussion
The results from this study demonstrate the close relationship between GABA, Glu, and Gln levels in the cortex of women across the menstrual cycle. As GABA levels systematically vary across the menstrual cycle, Glu levels mirror this change in the opposite direction. This phenomenon may be attributed to the metabolic production of GABA from Glu in the GABA shunt of the TCA cycle. The fact that the slope of the correlation between GABA and Glu was substantially greater for the PMDD subjects may suggest an alteration in the GABA shunt. The strong correlation between estradiol and Glu in the healthy controls indicates a possible interaction between neurosteroids and the regulation of Glu; this relationship appears to be missing and even possibly reversed in the PMDD subjects.

References