

# Mood changes correlate to changes in brain serotonin precursor trapping in women with premenstrual dysphoria

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## Abstract

The cardinal mood symptoms of premenstrual dysphoria can be effectively treated by serotonin-augmenting drugs. The aim of the study was to test the serotonin hypothesis of this disorder, i.e. of an association between premenstrual decline in brain serotonin function and concomitant worsening of self-rated cardinal mood symptoms. Positron emission tomography was used to assess changes in brain trapping of <sup>11</sup>C-labeled 5-hydroxytryptophan, the immediate precursor of serotonin, in the follicular and premenstrual phases of the menstrual cycle in eight women with premenstrual dysphoria. Changes in mood and physical symptoms were assessed from daily visual analog scale ratings. Worsening of cardinal mood symptoms showed significant inverse associations with changes in brain serotonin precursor trapping; for the symptom "irritable",  $r_s = -0.83$ , and for "depressed mood"  $r_s = -0.81$ . Positive mood variables showed positive associations, whereas physical symptoms generally displayed weak or no associations. The data indicate strong inverse associations between worsening of cardinal symptoms of premenstrual dysphoria and brain serotonin precursor (<sup>11</sup>C-labeled 5-hydroxytryptophan) trapping. The results may in part support a role for serotonin in premenstrual dysphoria and may provide a clue to the effectiveness of serotonin-augmenting drugs in this disorder but should, due to small sample size and methodological shortcomings, be considered preliminary.

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## 1. Introduction

Premenstrual dysphoric disorder (PMDD) is characterized by the cyclical occurrence of disabling mood symptoms in the luteal (premenstrual) phase of the menstrual cycle, with a profound impact on the afflicted

woman and her near environment (American Psychiatric Association, 1994). The cardinal symptoms are irritability, depressed mood, affective lability and impaired impulse control, all of which are effectively alleviated by drugs increasing brain serotonin activity (Eriksson, 1999). Randomised trials have shown selective serotonin reuptake inhibitors (SSRIs) to be effective pharmacological treatments in about 60% of women with PMDD (Rapkin, 2003), and these drugs are considered the

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most effective treatment known at present (Dimmock et al., 2000). This implies that reduced serotonergic activity might be one symptom-provoking factor in premenstrual dysphoria, supporting the “serotonin hypothesis” of the pathogenesis of the disorder, namely that worsening of self-rated premenstrual mood symptoms is associated with a concomitant decline in brain serotonin activity (Steiner and Pearlstein, 2000; Parry, 2001; Eriksson et al., 2002). Positron emission tomography (PET) was used to measure brain trapping of  $^{11}\text{C}$ -5-hydroxy-L-tryptophan ( $^{11}\text{C}$ -5-HTP), which when radiolabeled in the metabolically stable  $\beta$ -position is a marker of aromatic L-amino-acid decarboxylase (AAAD) activity (Bjurling et al., 1990; Hartvig et al., 1992, 1993; Lindner et al., 1997). Associations between changes in cardinal symptoms of PMDD and changes in brain  $^{11}\text{C}$ -5-HTP trapping from early (mid-follicular) to late (premenstrual) in the menstrual cycle were investigated. Primary end-points were associations between changes in the core symptoms of premenstrual dysphoria, “irritable” and “depressed mood”, and changes in  $^{11}\text{C}$ -5-HTP trapping in a large brain region representing the “whole brain” and in specific areas of the forebrain that are known to be involved in affective disorders (Ågren and Reibring, 1994; Brody et al., 2001; Davidson, 2002).

## 2. Methods

### 2.1. Participants

Eight women were recruited for the study, one through our gynecological admittance, and seven from subjects participating in a treatment trial published elsewhere (Landen et al., 2001). Inclusion criteria were: fulfillment of criteria A–C of PMDD as described in DSM-IV (American Psychiatric Association, 1994); fulfillment of criterion D by showing cyclicity of the core symptoms “irritability” and/or “depressed mood” in two of three visual analogue scale (VAS)-rated cycles. The inclusion criteria were thus a slightly modified version of the PMDD criteria of DSM-IV. The VAS instrument (0–100 mm) comprised the symptoms “irritability”, “depressed mood”, “tension”, “affective lability”, “food craving”, “breast tenderness” and “a sense of bloating”. A mean rating for the 5 days preceding menstrual onset should show an increase by at least 100% compared with that for days 6–10 from menstrual onset with a minimal luteal phase mean of 30 mm on the VAS scale. Additional inclusion criteria were fertile age, 18–45 years; regular menstrual cycles of 22–35 days; stated completion of birth-giving; effective non-hormonal contraception; and a normal gynecological examination within the

last year. Exclusion criteria were pregnancy or lactation; bleeding irregularity; and history of any major psychiatric disorder other than depression, including former or present drug abuse. Further exclusion criteria were ongoing depression or depressive episode within the past 2 years; ongoing somatic illness; and ongoing medication. The subjects also had to undergo a Structured Clinical Interview (First et al., 1995), performed by the study psychiatrist (I.M.), to rule out psychiatric axis I and axis II disorders (American Psychiatric Association, 1994). Subjects had a mean age of  $38.0 \pm 4.2$  years, with menstrual cycles of  $27.3 \pm 0.9$  days’ duration, and menstrual periods lasting  $5.6 \pm 0.9$  days. They had a mean pregnancy rate of  $2.4 \pm 1.9$  and a mean birth rate of  $1.8 \pm 1.3$ . They gave a history of premenstrual dysphoria of  $7.9 \pm 2.5$  years and at present of experiencing a mean number of  $7.1 \pm 2.1$  DSM-IV criterion A symptoms during  $9.5 \pm 3.1$  days of their menstrual cycles, with  $13.6 \pm 1.7$  days per cycle of feeling completely well. All subjects were right-handed. Three subjects were drug-naïve. Five subjects had tried a serotonin agonist for a short period of time: two buspirone, two nefazodone, and one buspirone and sertraline. Washout periods ranged from 2 to 12 months ( $6.6 \pm 4.5$ ). The subjects gave their informed consent to participate in the study, which was approved by the Human Ethics Committee of the Faculty of Medicine, Uppsala University and by the Radiation Hazards Committee of Uppsala University Hospital.

### 2.2. Symptom evaluation

The subjects performed daily prospective self-ratings of four negative and four positive mood variables and six somatic symptoms associated with PMDD, using a VAS instrument developed by Bäckström et al. and slightly modified from their first description (Hammarbäck et al., 1989). The assessed variables were irritability, depressed mood, fatigue, tension, happiness, energy, relaxation, friendliness, headache, bloating, breast tenderness, pelvic pain, craving for sweets and sexual desire. The subjects were instructed to mark total absence of a symptom as 0 mm on the VAS scale and the most intense form of the variable ever experienced by the individual as 100 mm.

### 2.3. Imaging

PET scans were performed with a GEMS PC2048-15B scanner (General Electric Medical Systems, Milwaukee, WI, USA) with an axial field of view of 10 cm producing 15 slices spaced 6.5 mm apart with an in-

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