

A PET study of 5-HT_{1A} receptors at different phases of the menstrual cycle in women with premenstrual dysphoria

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Abstract

The cause of premenstrual dysphoric disorder (PMDD) is largely unknown. It has been hypothesized that normal ovarian function triggers PMDD-related biochemical events within the brain and that serotonin plays an important role. In the present study, positron emission tomography (PET) and [*carbonyl*-¹¹C]WAY-100635 were used to examine serotonin 5-HT_{1A} receptors in a control group of women and in a group of women with PMDD. Two PET examinations were performed in each subject, one before (follicular phase) and one after ovulation (luteal phase). Each subject's menstrual cycle was confirmed by ultrasonography of the ovaries as well as with hormone levels in blood and urine. The 5-HT_{1A} binding potential was measured in six regions of interest and calculated according to the simplified reference tissue model. In the raphe nuclei, the 5-HT_{1A} binding potential changed from the follicular to the luteal phase of the menstrual cycle in asymptomatic controls. In women with PMDD, the observed change between phases was significantly smaller. The results are in concordance with previously reported challenge studies of 5-HT_{1A} receptor-mediated effects indicating different serotonergic responses between women with PMDD and controls. The study principally provides new support, *in vivo*, for a serotonergic dysregulation in women with PMDD.

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1. Introduction

Premenstrual dysphoric disorder (PMDD) is a cyclic mood disorder characterized by affective, behavioural and somatic symptoms that appear during the late luteal

phase of the menstrual cycle. PMDD is diagnosed in approximately 3% to 8% of women of reproductive age with irritability, tension, dysphoria and mood lability as the most prominent symptoms ([American Psychiatric Association, 1994](#)).

The cause of PMDD is largely unknown. Although many hypotheses have been put forward, the current consensus is that normal ovarian function, rather than hormone imbalance, represents a cyclic trigger for PMDD-related biochemical events within the central nervous system ([Schmidt et al., 1998](#)). Serotonin has been suggested

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as an important neurotransmitter in the pathophysiological mechanisms underlying PMDD. Abnormal serotonergic activity is associated with depression and anxiety disorders, with which PMDD seems to share significant features (Halbreich, 1995; Landen and Eriksson, 2003). In addition, selective serotonin reuptake inhibitors (SSRIs) have been found highly effective in the treatment of PMDD, as compared with other non-SSRI drugs, which have been reported to be less effective (Eriksson et al., 1995; Yonkers et al., 1997; Dimmock et al., 2000).

Among the subtypes of serotonin receptors characterized today, the 5-HT_{1A} receptors are of specific interest for premenstrual dysphoria. Bancroft et al. (1991) used L-tryptophan in a challenge test of growth hormone (GH), a response that is supposed to be mediated by 5-HT_{1A} receptors. They reported a blunted response in both menstrual phases in women with premenstrual symptoms as compared with controls. Additionally, Yatham (1993) reported a blunted prolactin response to buspirone challenge in the follicular phase of women with premenstrual dysphoria, suggesting 5-HT_{1A} receptor subsensitivity as a possible trait marker for this disorder.

Regional density of 5-HT_{1A} receptors in the living human brain is possible to investigate by using positron emission tomography (PET) and the highly specific radioligand [*carbonyl*-¹¹C]WAY-100635 (Farde et al., 1998). Previous PET studies using [*carbonyl*-¹¹C]WAY-100635 in patients with mood disorders have reported moderate to pronounced reductions of 5-HT_{1A} receptor binding in different brain areas including medial temporal cortex and dorsal raphe nucleus (Drevets et al., 1999; Sargent et al., 2000). PET studies of gender-specific effects on 5-HT_{1A} receptors binding have found higher 5-HT_{1A} receptor binding potentials in females than in males, and no age effect on 5-HT_{1A} receptors in women (Meltzer et al., 2001; Parsey et al., 2002). However, there are very few PET studies of the interaction between gonadal hormones and the serotonergic system in the human brain. Moses et al. (2000) used PET and [¹⁸F]altanserin to study the effects of estrogen and progesterone treatment in five postmenopausal women. Increased 5-HT_{2A} receptor-binding potentials were found in widespread areas of the cerebral cortex following hormonal administration relative to baseline values. To date, no PET study has been published on the effects of phases of the menstrual cycle on 5-HT_{1A} receptor binding.

Based on the previous literature, we hypothesized that there might be differences in serotonin receptor densities between women with PMDD and asymptomatic controls. The aim of the present study was thus to examine the 5-HT_{1A} receptor-binding density in women with PMDD compared with asymptomatic controls, at

two different phases of the menstrual cycle, by using PET and the selective radioligand [*carbonyl*-¹¹C]WAY-100635.

2. Methods and materials

2.1. Overall study design

Each subject took part in two PET examinations with [*carbonyl*-¹¹C]WAY-100635 for measurements of 5-HT_{1A} receptor-binding potential (BP). PET I was performed during the follicular phase of the menstrual cycle (ovulation days – 10 to – 3), while PET II was performed during the late luteal phase (ovulation days + 6 to + 13). The late luteal phase is the period of the menstrual cycle for symptom manifestation in women with PMDD. Since the definition of PMDD requires ovulation and a functioning corpus luteum, each subject was assessed with regard to the timing of ovulation, by gynaecological examination, blood and urine hormone assays. All participants filled out daily rating forms prospectively for at least two consecutive cycles, one of which was the month of the PET experiments.

2.2. Subjects

Five outpatients (age: 26–39 years, mean age: 32.4 ± 6.2) with PMDD and five female control subjects (age: 24–39 years, mean age: 30.2 ± 7.6) were recruited. Inclusion criteria were history of regular menstrual cycles, physical health confirmed by medical history, physical examination and routine laboratory tests, negative urine pregnancy test, and no use of psychotropic or hormonal drugs (including oral contraceptives) for the past 6 months. All subjects were screened by a psychiatric clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The exclusion criteria for women with PMDD were the presence of any other Axis I or an Axis II disorder. Control subjects were not included if they had a personal or family history of psychiatric disorder. The diagnosis of premenstrual dysphoric disorder was based on the DSM-IV research criteria, and was confirmed through prospective daily symptom ratings on a 100-mm Visual Analogue Scale for at least two consecutive menstrual cycles. Premenstrual dysphoric women had to have a greater than 50% increase in symptom severity of irritability, depression, or anxiety, in the luteal phase of the cycle compared with the follicular phase on the Visual Analogue Scale.

The study was approved by the Ethics and the Radiation Safety Committees of Karolinska Hospital, and all subjects participated after giving informed consent.

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