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Differential response to estrogen challenge test in women with and without premenstrual dysphoria

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Summary This study tested the hypothesis that brain sensitivity to normal fluctuations in gonadal hormones is increased in women with premenstrual dysphoria. For this purpose, the effect of a common gonadal hormonal challenge on the sensitivity of the brain was investigated in 13 women with premenstrual dysphoria and 12 asymptomatic controls. The estrogen challenge test, comprising estradiolbenzoate 0.04 mg/kg, was given as an intramuscular gluteal injection between 0700 and 1000 h on day 3 or 4 of the menstrual cycle; blood was sampled at 0, 0.6, 6.5, 24, 32, 48, 56, 72, 96, 120, and 144 h and analyzed for estradiol, FSH and LH. Serum estradiol levels after the injection and the corresponding FSH responses were similar between the study groups; however, the LH responses were significantly different. Women with premenstrual dysphoria had a relatively stronger negative feedback response ($p=0.014$) up to the point of nadir LH levels (maximal negative feedback), but displayed higher LH levels at the nadir ($p=0.01$), more LH surge-like reactions ($p=0.047$), and a 50% higher area under the curve (AUC) for LH ($p=0.03$) than controls. The LH response in women with premenstrual dysphoria was related to the VAS-rated symptoms; the negative increment (AOC) correlated to luteal phase 'bloating' ($r_s=0.73$; $p=0.0069$) whereas the AUC of LH correlated to 'irritability' ($r_s=0.58$; $p=0.040$). A significant interaction term between study group and changes in LH during the negative feedback phase (32–0 h), with regard to luteal phase 'irritability' was found (test for interaction $p=0.005$). For the premenstrual dysphoria group, ratings of 'depressed mood' were related to baseline FSH levels ($r_s=0.60$; $p=0.034$), and to the AUC of FSH during the negative feedback phase ($r_s=0.58$; $p=0.043$).

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Women with premenstrual dysphoria displayed a gonadotrophin reponse to estradiol challenge that differed from that of controls, and was correlated to symptom severity.

1. Introduction

The majority of menstruating women perceive mood symptoms to some degree premenstrually (Andersch et al., 1986; Hallman, 1986; Warner & Bancroft, 1990; Hylan et al., 1999; Sveindottir & Backstrom, 2000; Hourani et al., 2004), and about 10% experience mood symptoms motivating medical treatment (Andersch et al., 1986). From two to eight percent of women with spontaneous menstrual cycles suffer from premenstrual mood symptoms severe enough to socially and/or professionally disable them during the 1–2 weeks prior to menstrual bleeding each month (Rivera-Tovar & Frank, 1990; Reid, 1991; Ekholm & Backstrom, 1994; Cohen et al., 2002; Halbreich et al., 2003). Research findings indicate that hormonal substances secreted cyclically by the ovaries elicit the disorder (Backstrom et al., 1983; Hammarback & Backstrom, 1988; Steiner, 1992; Steiner & Pearlstein, 2000) but the underlying mechanisms are still unclear (Schmidt et al., 1998). No consistent differences in ovarian hormonal levels or patterns of secretion between women with debilitating mood symptoms and symptom-free controls have been identified (Rubinow & Schmidt, 1995; Schmidt et al., 1998; Kessel, 2000). However, the sensitivity of the brain to normal cyclic hormonal perturbations may differ and determine whether a woman will experience mood symptoms or not (Backstrom, 1992; Halbreich, 1995; Schmidt et al., 1998; Steiner & Pearlstein, 2000). The study was prompted by the findings of differences in gonadotropin responses to surgical corpus luteectomy in women with premenstrual syndrome compared to asymptomatic controls (Backstrom et al., 1985), findings coherent with a more sensitive hypothalamo-pituitary unit in women experiencing premenstrual dysphoria.

The aim of this study was to test whether the sensitivity of the brain to a standardized gonadal steroid hormone challenge, estradiol, injected intramuscularly in the early follicular phase (Shaw et al., 1975), differed between women with severe premenstrual mood symptoms and symptom-free controls. We hypothesized that the brains of women with premenstrual dysphoria would be more sensitive to the estradiol challenge than those of controls, as demonstrated by a faster and stronger negative feedback effect on the release of luteinizing hormone (LH) and, predominantly, follicle-stimulating hormone (FSH), and a faster and stronger positive feedback effect on the release of FSH and, predominantly, LH; we also hypothesized that the extent of the feedback response would correlate with the severity of mood symptoms self reported during menstrual cycles before the challenge.

2. Methods

2.1. Subjects

Twenty-five subjects were recruited for the study: 13 cases and 12 controls. Cases were recruited consecutively from eligible women seeking medical help for intractable premenstrual mood symptoms at the Gynecological Admissions department, Uppsala University Hospital.

Inclusion criteria for cases were: a history of at least two years of recurrent intractable mood symptoms during the luteal phase of the menstrual cycle, with associated effects on social functioning and/or work; a documented increase of at least 100% in the symptoms of 'irritability' and/or 'depressed mood', from the follicular phase (values obtained from the mean visual analog scale [VAS] rating for days 6–10 from the first day of menstruation) to the luteal phase (mean rating for days 5–1 before the start of menstruation), in one or both of two VAS-rated menstrual cycles; a luteal phase mean rating (for days 5–1 before the start of menstruation) for the symptoms 'irritability' and/or 'depressed mood' exceeding 30 mm on the 0–100 mm VAS scale; current physical and mental health as assessed by clinical evaluation, including normal findings at gynecological examination, and spontaneous regular menstrual cycles of 21–35 days' duration. Exclusion criteria were: pregnancy, breast-feeding, steroid hormonal treatment (other than thyroxin substitution in one woman with well managed congenital hypothyroidism, who was accepted for participation), current medication that might interfere with the study results, a history of chronic mental illness or of substance