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Allopregnanolone and mood disorders

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ABSTRACT

Certain women experience negative mood symptoms during the menstrual cycle and progesterone addition in estrogen treatments. In women with PMDD increased negative mood symptoms related to allopregnanolone increase during the luteal phase of ovulatory menstrual cycles. In anovulatory cycles no symptom or sex steroid increase occurs. This is unexpected as positive modulators of the GABA-A receptor are generally increasing mood. This paradoxical effect has brought forward a hypothesis that the symptoms are provoked by allopregnanolone the GABA-A receptor system. GABA-A is the major inhibitory system in the brain. Positive modulators of the GABA-A receptor include the progesterone metabolites allopregnanolone and pregnanolone, benzodiazepines, barbiturates, and alcohol. GABA-A receptor modulators are known, in low concentrations to induce adverse, anxiogenic effects whereas in higher concentrations show beneficial, calming properties. Positive GABA-A receptor modulators induce strong paradoxical effects e.g. negative mood in 3–8% of those exposed, while up to 25% have moderate symptoms thus similar as the prevalence of PMDD, 3–8% among women in fertile ages, and up to 25% have moderate symptoms of premenstrual syndrome (PMS). The mechanism behind paradoxical reaction might be similar among them who react on positive GABA-A receptor modulators and in women with PMDD. In women the severity of these mood symptoms are related to the allopregnanolone serum concentrations in an inverted U-shaped curve. Negative mood symptoms occur when the serum concentration of allopregnanolone is similar to endogenous luteal phase levels, while low and high concentrations have less effect on mood. Low to moderate progesterone/allopregnanolone concentrations in women increases the activity in the amygdala (measured with fMRI) similar to the changes seen during anxiety reactions. Higher concentrations give decreased amygdala activity similar as seen during benzodiazepine treatment with calming anxiolytic effects. Patients with PMDD show decreased sensitivity in GABA-A receptor sensitivity to diazepam and pregnanolone while increased sensitivity to allopregnanolone. This agrees with findings in animals showing a relation between changes in alpha4 and delta subunits of the GABA-A receptor and anxiogenic effects of allopregnanolone.

Conclusion: These findings suggest that negative mood symptoms in women with PMDD are caused by the paradoxical effect of allopregnanolone mediated via the GABA-A receptor.

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Abbreviations: GABA-AR, gamma-butyric-acid-A receptor; GABA-A, gamma-butyric-acid-A; PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome; fMRI, functional magnetic resonance imaging; GAMS, GABA-A receptor modulating steroids; CNS, central nervous system; MPA, medroxyprogesterone-acetate; HRt, hormone replacement therapy; mPFC, medial prefrontal; OFC, orbitofrontal cortex; SEV, saccadic eye velocity.

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1. Introduction

Mood disorders are common health problems especially affecting women in reproductive ages. Depression is the most common condition with lifetime prevalence between 14 and 21% (Wittchen et al., 1992; Kessler et al., 1994). Equally common is menstrual cycle related mood changes appearing in 3–8% in its very severe form as premenstrual dysphoric disorder (PMDD). The less severe premenstrual syndrome (PMS) are as common as up to 25% of women in fertile ages (Sveinsdóttir and Bäckström, 2000; Halbreich et al., 2003; Epperson et al., 2012; Hartlage et al., 2012). In this paper, we are discussing if neuroendocrine factors such as neuroactive steroids or natural GABA-A receptor active modulators (GAMS) are involved in the symptom provocation and in what way and why only a subset of women react negatively to the sex and stress steroids produced during the luteal phase of the menstrual cycle. A deeper understanding of the underlying mechanisms related to the cyclical mood changes is of importance as the on and off situation in steroid production during the menstrual cycle gives an opportunity to study CNS effects with the same individual when the endogenous production is high and low.

2. Allopregnanolone production in women

That allopregnanolone varies during ovulatory menstrual cycle in a regular fashion is an unabated fact even though individual variations occur. (Nyberg et al., 2007). The levels in serum increase during the luteal phase of the menstrual cycle and the increase is noted within the brain (Bixo et al., 1997). However, in anovulatory menstrual cycle the organ producing allopregnanolone, the corpus luteum of the ovary is not formed, and that result in low and stable allopregnanolone levels throughout the menstrual cycle (Ottander et al., 2005). Certain women especially they who suffer from premenstrual dysphoric disorder (PMDD) show cyclical mood changes with increased negative mood during the luteal phase reaching a maximum during the last days of the menstrual cycle or during the first days of the menstrual bleeding (Fig. 1).

Allopregnanolone and some similar compounds like pregnanolone are produced in parallel with progesterone during the menstrual cycle (Nyberg et al., 2007; Innala et al., 2012). However, neuroactive steroids, such as allopregnanolone, can be synthesized de novo in the central nervous system (Stoffel-Wagner, 2001), but in fertile women the major contributor to endogenous levels of allopregnanolone is the corpus luteum of the ovary (Wang et al., 1996; Ottander et al., 2005; Bixo et al., 1997; Genazzani et al., 1998). In fertile women plasma levels of allopregnanolone are approximately 0.2–0.5 nmol/L in the follicular phase and up to 4 nmol/L in the luteal phase. In the third trimester of a pregnancy these levels increase up to more than 100 nmol/L (Biciková et al., 1995; Luisi et al., 2000).

3. Relation between serum allopregnanolone concentrations and mood symptoms

The relation between the allopregnanolone rise during the luteal phase and symptom development in PMDD/PMS is obvious (Bäckström et al., 1983). The symptom starts at the time of ovulation, increase in parallel with the rise in serum progesterone during the luteal phase. The symptom severity reaches a peak during the last 5 premenstrual days or the first days of menstruation. When allopregnanolone reached the lowest level the symptoms decline and disappear 3–4 days after the nadir is reached (Fig. 1, Bäckström et al., 1983, 2003). However, the endocrine progesterone receptor antagonist (RU486) was not able to block the premenstrual symptoms (Chan et al., 1994). In anovulatory cycles, spontaneous or induced the corpus luteum is not formed and progesterone or allopregnanolone is not produced. In such situation the symptom cyclicity disappears (Hammarbäck and Bäckström, 1988; Hammarbäck et al., 1991; Mortola et al., 1991). There is a lag time of 4–5 days between peak of luteal steroids and peak of symptoms indicating that the symptom development takes some time like if a change in sensitivity occurs during the luteal phase (Fig. 2, Wang et al., 1996). The lag time between the allopregnanolone peak and symptom peak suggests that a protein synthesis occur and is of importance for the symptom development.

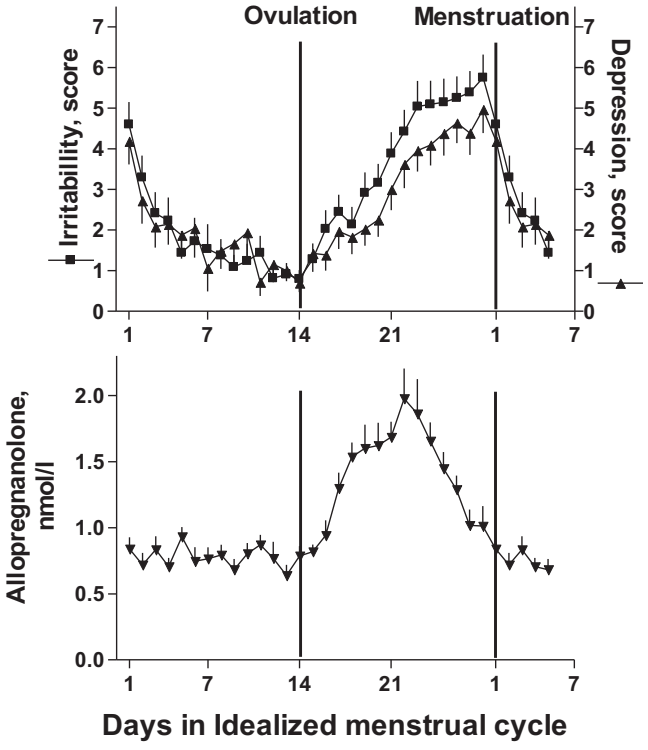

Fig. 1. Symptom and allopregnanolone relation during 38 menstrual cycles in 19 patients with PMDD. Irritability and depression score curve correlates best with allopregnanolone serum concentration with 3 days latency after allopregnanolone curve.