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Premenstrual Dysphoric Disorder in relation to Neuroactive Steroids and Alcohol

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ABSTRACT

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Introduction: Premenstrual Dysphoric Disorder (PMDD) is a condition that affects about 2-6% of women of reproductive age. The relation to ovarian steroids is apparent as symptoms are absent during anovulatory cycles. Neuroactive steroids like allopregnanolone have effect in the brain and on brain function and have been proposed to play an important role for the symptomatology of premenstrual symptoms and in the interaction between the $GABA_A$ receptor and alcohol. High doses of alcohol elevate allopregnanolone levels both in rats and humans. Allopregnanolone is a positive modulator of the $GABA_A$ receptor with sedative, anxiolytic and anticonvulsant effect in both human and animals.
Aims: The aim was to investigate if a low dose of GnRH agonist (buserelin) is effective for the treatment of PMDD and if allopregnanolone serum levels during treatment are associated to symptom severity. Furthermore, the studies aimed at investigating the effect of a low dose of alcohol upon saccadic eye movements in women with PMDD and control subjects in different phases of the menstrual cycle, and to evaluate if there was a difference in response to alcohol between men and healthy women. We also wanted to see if this low dose of alcohol could have an effect on serum allopregnanolone levels in women with PMDD and control subjects in the follicular and luteal phases of the menstrual cycle.
Methods: The effect of low dose (100µg) of GnRH agonist (buserelin) on premenstrual symptoms was evaluated in a randomized, placebo-controlled, double-blinded crossover trial. 27 PMDD patients were randomized to either GnRH agonist intranasally once a day or placebo for two months before the crossover. The main outcome measure was the daily symptom ratings for mood and physical symptoms made by the patients. In a subgroup of 12 women, grouped as buserelin responders and placebo responders, luteal phase serum progesterone, allopregnanolone, and pregnanolone was measured together with daily ratings for mood and physical symptoms. Alcohol responsiveness was measured in PMDD patients, female control subjects and men by comparing the effect of a low dose (0.2g/kg) of intravenous alcohol or placebo infusion upon saccadic eye movements. Blood samples for measurement of allopregnanolone and cortisol were taken throughout the alcohol/placebo challenges.
Results: Low dose GnRH agonist was effective as treatment of premenstrual irritability and depression. Anovulatory cycles were confirmed in 56% of the subjects, particularly in older women. Buserelin as well as placebo responders displayed decreased allopregnanolone and progesterone serum concentrations in parallel with symptom improvement. PMDD patients displayed blunted saccadic eye movement response to alcohol infusion, especially in the luteal phase. Control subjects did not change their response to alcohol between cycle phases. We found no difference in saccadic eye movement sensitivity to alcohol between males and females. Allopregnanolone levels significantly decreased in the luteal phase following the alcohol infusion.
Conclusions: Low dose GnRH agonist is effective in treatment of premenstrual depression and irritability but is likely to induce anovulation with increasing age. Independent of whether buserelin or placebo treatment was given decreased levels of allopregnanolone appear to be related to symptom improvement. Women with PMDD have altered saccadic eye movement sensitivity in response to alcohol, particularly in the luteal phase. The low dose of alcohol did not induce any difference in saccade measurements between males and females. Low dose of alcohol does not result in increased peripheral levels of allopregnanolone.
Key words: Premenstrual Dysphoric Disorder, GnRH-agonist, progesterone, allo-pregnanolone, alcohol, saccadic eye velocity.