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$GABA_A$ Receptor-Modulating Steroids in Relation to Women's Behavioral Health

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Abstract In certain women, increased negative mood relates to the progesterone metabolite, allopregnanolone (allo), during the luteal phase of ovulatory menstrual cycles, the premenstrual dysphoric disorder (PMDD). In anovulatory cycles, no symptom or sex steroid increase occurs but symptoms return during progesterone/allo treatment. Allo is a potent $GABA_A$ receptor-modulating steroid and as such is expected to be calming and anxiolytic. A relation to negative mood is unexpected. However, this paradoxical effect can be induced by all $GABA_A$ receptor modulators in low concentrations whereas higher concentrations are calming. The severity of the mood symptoms relate to allo in an inverted U-shaped curve at endogenous luteal-phase serum concentrations. Allo's effects on the $GABA_A$ receptor can be antagonized by isoallopregnanolone (ISO), an antagonist to allo. ISO has also been used in a preliminary clinical trial on PMDD ameliorating symptoms with good effect in PMDD patients.

Keywords $GABA_A$ receptor-modulating steroids · Premenstrual dysphoric disorder · Mood symptoms

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Introduction

One very obvious relation between steroids in serum and mood symptoms in women is the symptom variations during the menstrual cycle. The sex hormones estradiol and progesterone show regular predictable changes during the menstrual cycle. In parallel with progesterone, the $GABA_A$ receptor-modulating steroids allopregnanolone (allo) and pregnanolone increase in serum [1, 2] and are produced by the corpus luteum of the ovary [3]

Negative Mood Symptoms are Related to $GABA_A$ Receptor-Modulating Steroid Concentrations in Serum

Conditions where there is evidence for the interaction between mood, steroids, and CNS function are the premenstrual dysphoric disorder (PMDD) [4] and the less severe condition premenstrual syndrome (PMS) [5]. In PMDD/PMS, the symptoms develop during the luteal phase of the menstrual cycle [6, 7, 8••]. The symptoms start at the time of ovulation, and the severity increases in parallel with the rise in serum progesterone and it's $GABA_A$ receptor-modulating metabolite allo (Fig. 1). The symptom severity reaches a maximum during the last five premenstrual days or at the first day of menstruation and usually disappears within 3–4 days into the next menstrual cycle. During the postmenstrual phase, there is a period of well-being related to the estradiol peak [8••]. The close relation between the presence of mood symptoms and the steroid production from the corpus luteum of the ovary suggests that there is a symptom-provoking factor produced by the corpus luteum of the ovary. In anovulatory cycles, spontaneous or induced, the corpus luteum is not formed and progesterone or allo is not produced. In such cycles, the premenstrual symptom cyclicity disappears [10, 11••, 12]. We know that the increase in serum concentration due to

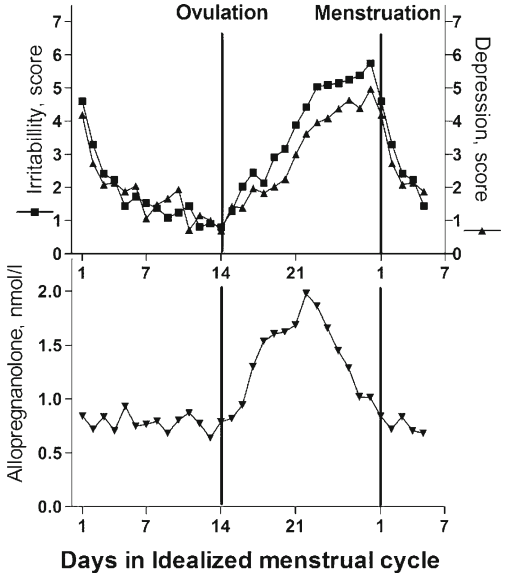

Fig. 1 PMDD core symptoms and allopregnanolone concentrations during an idealized menstrual cycle in women with PMDD. Data are centered on the day of menstrual bleeding onset and ovulation. Irritability and depression scores were rated using a Likert rating scale. The symptoms correlate best with allopregnanolone serum concentration with 3 days latency after allopregnanolone curve. From [9], with permission from Elsevier

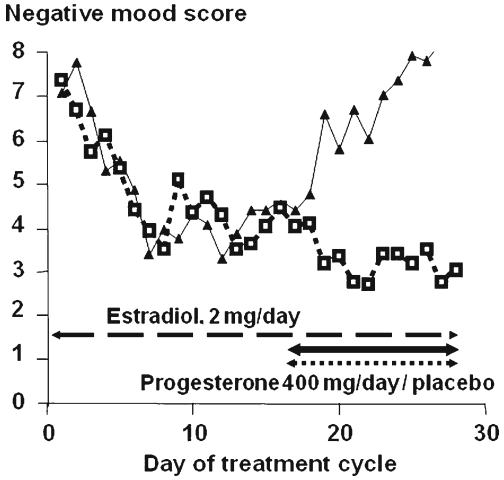

Fig. 2 Mood changes in postmenopausal women taking sequential hormone replacement therapy in a cross-over double-blind controlled study. Progesterone but not placebo is accompanied with negative mood symptoms. From [16], with permission from Elsevier

production from the corpus luteum is noted in the brain even though the concentration varies depending on the brain region [13]. The regional brain distribution of allopregnanolone showed the highest levels in the substantia nigra, and the basal hypothalamus was significantly higher than in all other investigated areas except the amygdala. Taken together, the brainstem, basal ganglia, and cerebellum showed significantly higher concentrations during the luteal phase compared to postmenopausal controls. The other areas showed numerical differences but did not reach significance probably due to low sample number as only four (4) women were obtained in the respective groups [13]. That the symptom-provoking factor could be progesterone or allo is shown by the fact that the symptoms reappear in PMDD women where the endogenous ovarian steroid production is inhibited, with gonadotropin-releasing hormone agonist treatment (GnRH), but estrogen and progesterone ad back is given. Women with PMDD then develop negative mood symptoms during the progesterone/allo period. Normal control women do not react on the progesterone/allo ad back contrary to women with PMDD [14, 15]. Similar increase in negative mood is noted in postmenopausal women receiving cyclical estrogen progesterone therapy (Fig. 2), [17••]. In the study by Schmidt et al. [14], both estradiol alone and progesterone alone provoked symptoms in anovulatory leuprolide-treated women. This is contrary to results by Segerblad et al. where estrogen-alone treatment was related to a period of well-being [15]. Also in postmenopausal women, estrogen alone is related to periods of well-being while estrogen combined with progesterone gives increased negative mood [16, 18]. During the menstrual cycle in women with PMDD, the period around the preovulatory estradiol peak is a period of well-being, that is, the women feel as best [8••]. However, estrogen in combination with progesterone/allo seems to have a different effect. A higher dosage of estrogen together with progestogen is related to worse symptoms [18], and in a placebo-controlled study, estrogen treatment during the luteal phase worsened the symptoms [19]. The reason why Schmidt and coworkers obtained a worsening of PMDD symptom by estradiol alone is puzzling and has not been repeated in other studies.

Paradoxical Response to Positive $GABA_A$ Receptor-Modulating Steroids

Normally positive $GABA_A$ receptor modulators like benzodiazepines, alcohol, and barbiturates are anxiolytic, induce sedation, calmness, and have antiepileptic effects. Why there is a relation between the luteal-phase increase in allo after ovulation and the development of negative mood is difficult to understand as allo should be anxiolytic like benzodiazepines. The answer seems to be the fact that all positive $GABA_A$ receptor modulators like benzodiazepines, barbiturates, alcohol, and allo have paradoxical anxiogenic effects under certain circumstances in certain individuals. The compounds are not always showing the expected effect but instead induce the opposite effect such as irritability and anxiety. This reaction is called a paradoxical reaction or a paradoxical effect. The paradoxical symptoms induced by these $GABA_A$ receptor-active drugs are irritability, aggression, anxiety, depression, and other symptoms also known to occur during the luteal phase in women with PMDD [4] or PMS [5] and during progestogen treatments in postmenopausal hormone-replacement therapy [16, 20]. For example, certain patients

react to low-dosage benzodiazepines with irritability, aggression, confusion, violence, and impaired impulse control but have a normal anxiolytic calming effect on higher dosages [21–23]. Human reports indicate that strong negative symptoms are induced in 3–6 % of individuals and moderate symptoms in 20–30 % [24, 25]. Interestingly, the prevalence of premenstrual dysphoric disorder among women in reproductive age is in the similar range, 3–8 % [4], and 25–35 % has milder symptom severity in PMS [5, 26]. Weinbroum et al. reported a 10.2 % incidence of paradoxical events to midazolam in patients who underwent surgery during a 3-month period. They showed that benzodiazepine receptor antagonist treatment effectively reversed the paradoxical behaviors [25]. The paradoxical effect can also be induced by barbiturates, e.g., during evaluation of epileptic patients for epilepsy surgery [27, 28]. Alcohol has also been associated with paradoxical effects like increased irritability and aggression. A number of human studies have reported increased aggression after alcohol consumption [29, 30].

Studies on mood effects of oral progesterone treatment show an inverted U-shaped bimodal pattern in the negative mood severity to allo concentration. Postmenopausal women with oral progesterone treatment developed allo concentrations in physiological luteal-phase concentrations and responded with the highest negative mood scores. The mood deterioration is less evident at lower and higher concentrations (Fig. 3), [17••]. In postmenopausal women, the bimodal effect has been noted with different dosages of medroxyprogesterone (MPA) and natural progesterone in hormone-replacement therapy (HRT). The women feel worse on a lower dosage than a higher dosage or placebo [16, 20]. A similar difference between high and low progestogen dosages has also been noted for oral contraceptives [31].

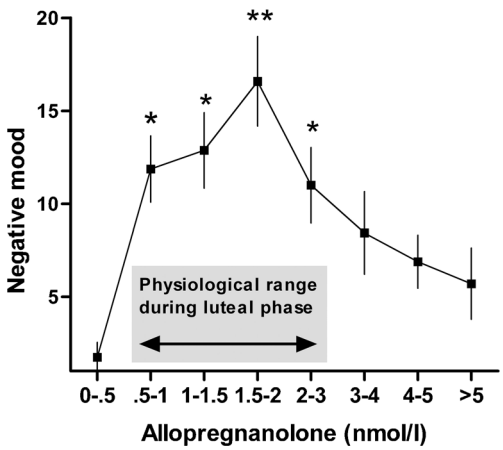

Fig. 3 Negative mood ratings from the same day as blood samples were taken. Symptoms increase related to increasing serum allopregnanolone in postmenopausal women taking oral progesterone. The *shaded area* indicates the normal allopregnanolone range during the luteal phase of the menstrual cycle. From [17••], with permission from Springer

An inverted U-shaped relation between allo, alcohol, and midazolam dosage and irritability/aggression has also been noted in rats [32, 33]. In rats, the benzodiazepine-heightened aggressive behavior induced by midazolam or triazolam was also antagonized by flumazenil and the $GABA_A$ receptor antagonists β-CCt and 3-PBC [33, 34]

Indications of a paradoxical and inverted U-shaped relation between allo and negative mood symptoms is also seen in fMRI studies in women and will therefore be mentioned here. Especially the amygdale has been studied in relation to emotional experiences and is therefore of interest to study. The amygdale responses to fearful and aversive pictures after oral progesterone administration has been studied at moderate and high allo concentrations. Oral progesterone is metabolized to allo in a high degree, and the serum concentration of allo obtained is equal to that of progesterone [35]. Administration of progesterone, giving plasma concentrations in the upper luteal-phase range as when the negative mood symptom in patients are highest, increases the neural response to angry and fearful faces in the amygdale compared to placebo [36••]. A reduced fMRI response would be expected together with an anxiolytic effect similar to the benzodiazepine response in dosages giving anxiolytic effects. Benzodiazepines giving an anxiolytic effect also give reduced fMRI responses to angry and fearful face stimuli [37]. However, even higher allo concentrations, in the pharmacological sedative and late pregnancy range, are associated with a decrease in amygdale reactivity similar to the benzodiazepine fMRI effect when anxiolysis is induced. It seems as if allo at this concentration has passed the peak of the paradoxical effect and the concentration is in the anxiolytic range. The opposite responses in amygdala at low compared to high allo concentrations support the hypothesis of a bimodal paradoxical effect of allo [38••]. The increased amygdale response in the fMRI studies was observed when allo levels were in the luteal phase or early pregnancy range [1, 39], whereas higher concentrations gave a different response [38••].

Sensitivity in the $GABA_A$ System to Different $GABA_A$ Modulators in PMDD

It seems thus that a subset of individuals is very sensitive to low doses or concentrations of allo and responds with severe adverse emotional reactions when provoked. There are now increasing neuroimaging data available on menstrual cycle and sex steroid influence on brain activity under normal physiological situations and in disorders. An excellent review of studies on PMDD/PMS is available elsewhere, and that topic is over the scope of this review [40]. There is evidence that the sensitivity in the brain for steroids differs between PMS/PMDD patients and controls. Saccadic eye velocity (SEV) recorded by electrooculography is a measurement of functional $GABA_A$ receptor activity, and the method could be used in challenges with different $GABA_A$ receptor modulators [41].

In patients with PMDD, a decreased sensitivity to diazepam but an increased sensitivity to allo has been shown in the SEV model. In studies on women with PMDD and controls, relapse of symptoms did not occur in normal women or in PMS/PMDD women during placebo treatment, but the symptoms appear during the progestogen treatment in women with PMDD [15]. Neuroimaging studies show different responses in women with PMDD compared to women without any menstrual-cycle-related mood changes [42, 43].

In PMS/PMDD patients but not in healthy controls, SEV and the sedative response to intravenous diazepam and alcohol is reduced in the luteal phase compared to follicular phase [44–46]. In addition, patients with severe symptoms were less sensitive to the given pregnanolone or benzodiazepine compared to patients with more moderate symptoms [44, 47].

Possible Treatments Related to the GABA-Hypothesis

As has been mentioned above, allo seems to be involved in the induction of negative mood symptoms in women with PMDD. If the hypothesis is correct, a blockade of the allo effects on the $GABA_A$ receptor should be a possible treatment of PMDD. Studies of allo in vitro on the $GABA_A$ receptor activity and in vivo animal studies of sedation have shown that allo-induced effects can be inhibited by isoallopregnanolone (ISO) which also is an endogenous steroid isomer of allo [48–50]. In an experimental study, we have investigated if ISO can antagonize allo-induced CNS effects in healthy female volunteers, by using measurements of SEV and self-rated sedation. Healthy women were studied on three separate occasions, after being given allo alone or allo in combination with one of two ISO doses. Allo administration decreased SEV and induced sedation as expected, and these effects were diminished by simultaneous ISO administration. The ISO effect seems also to be stronger for SEV than for sedation [51••]. These effects were observed already at an ISO dose exposure that was approximately half of that of allo. In a recently performed, double-blind placebo controlled clinical trial using ISO as treatment for PMDD, preliminary data show a significant amelioration of PMDD symptoms compared to placebo in women with PMDD [52].

ISO is a 3beta-hydroxy isomer of allo and is also an endogenous steroid. ISO has no effect by itself on the $GABA_A$ receptor or on any of the steroid hormonal receptors [48, 49, 53]. The endogenous concentrations of ISO in normal women vary with the menstrual cycle and are about four times higher during mid-luteal phase (1.23±1.12 mean±SD, nanomol/L) compared to the follicular phase. The concentration of ISO both in the follicular and luteal phases is about half (54–57 %) the concentration of allo [54], but there are no ISO concentrations measured in patients with PMDD. In women with chronic fatigue syndrome, both allo and ISO are increased in the serum but the increase of ISO was greater than for allo; one speculative explanation is that ISO is increased to compensate for the increased sedative effect of allo [55]. There is also a study on depressed patients, mixed sexes, and menstrual cycle phases. The results are difficult to interpret, but ISO seems to be increased while allo seems not to be increased [56]

Other Behavioral Health Conditions Common in Women and Related to $GABA_A$ Modulating Steroids, e.g., Burnout Syndrome and Post-Traumatic Stress Disorder (PTSD)

As mentioned above, low concentrations or doses of positive $GABA_A$ receptor modulators give severe adverse emotional reactions in a subset of individuals (3–6 %) and moderate reactions in up to 20–30 %. In PMDD/PMS, the symptoms are known to occur during the luteal phase in women. However, allo is also always de novo synthesized in the central nervous system, and the CNS production is regulated differently from the gonadal and adrenal production [13, 57]. Changes in the CNS production have implications for the GABAergic function in the brain [58]. This suggests that there can be other CNS-related conditions that are influenced by allo. We have studied women with burnout syndrome, and they show an increased sensitivity to allo compared to healthy controls [59]. Women with post-traumatic stress syndrome are, however, less sensitive to allo than healthy controls and also less sensitive to benzodiazepine challenge suggesting that they have a changed $GABA_A$ receptor function which is different from women with burnout syndrome [60].

There are indications that early life emotional trauma is related to an increased risk of developing PMDD/PMS [61]. Early life stress history is also a risk factor for developing PTSD after a trauma later in life [62]. Women developing PTSD after a rape show a decreased sensitivity to benzodiazepines. PMS/PMDD patients and panic disorder patients are also less sensitive to benzodiazepines [45, 60, 63] suggesting that there might be a common $GABA_A$ receptor change in these three disorders.

Conclusion

Here we give some evidence and examples on mental effects induced by $GABA_A$ receptor-modulating steroids. This is a new mechanism and field of mechanisms in especially women's mental health and behavior. Interesting is that treatments for these disorders induced by $GABA_A$ receptor-active compounds is on the way, and a new area for treatments of mental disorders opens up, however, not only in women but also in men.

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Compliance with Ethics Guidelines

Conflict of Interest Torbjörn Bäckström is a share holder in Umecrine AB.

Marie Bixo has nothing to declare.

Jessica Strömberg has nothing to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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