Chapter 20
Neuroactive Steroids in Brain and Relevance to Mood

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Abstract Depression and anxiety often affect women in relation to reproductive events like menarche, premenstrual periods, post-partum and perimenopause. A prominent example of the interaction between mood, neuroactive-steroids and the GABA system is premenstrual dysphoric disorder (PMDD). Severe premenstrual negative mood symptoms occur in 3–8% of women. Sex and stress hormones are metabolized to neuroactive steroids with effects on brain function as positive modulators of the $GABA_A$ receptor (called GABA-steroids) similar to benzodiazepines, barbiturates and alcohol. One example of a neuroactive sex steroid is allopregnanolone, and other GABA-steroids, are produced within the brain, by the adrenals at stress and from the ovary during the menstrual cycle. Animal and human studies show that benzodiazepines, barbiturates, alcohol and allopregnanolone have a bimodal effect on behavior. In high dosages or concentrations the positive $GABA_A$ receptor modulators are CNS depressants, anesthetic, and anxiolytic, whereas in certain sensitive individuals low concentrations instead of being anxiolytic cause severe anxiety, irritability, aggressiveness and depressive mood in 3–6% of individuals, and moderate symptoms in up to 30%. Low concentrations of GABA-steroids are found endogenously during the luteal phase and induce adverse emotional reactions. In women with PMDD/PMS this paradoxical effect of neuroactive steroids seems to provoke negative mood symptoms as tension, irritability and depression. The mechanism behind the effect is called disinhibition that acts together with tolerance development by $GABA_A$ receptor active substances. Effective treatments are inhibition of ovarian steroid production or changing the CNS response to neuroactive steroids.

Keywords $GABA_A$ receptor, premenstrual dysphoric disorder, negative mood, menstrual cycle, allopregnanolone, progesterone, paradoxical effect, gaba-steroids

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Abbreviations CNS central nervous system; fMRI functional magnetic resonance imaging; GABA gamma-aminobutyric acid; $GABA_A$ one receptor for GABA; GABA-steroids positive modulators of $GABA_A$ receptor; HT hormone therapy; MPA medroxyprogesterone; MRI magnetic resonance imaging; PMDD premenstrual dysphoric disorder (PMDD); PMS premenstrual syndrome; RU486 mifepristone

20.1 Introduction

Mood disorders are common health problems affecting women, especially during the reproductive years. Women are about two times as likely as men to report a lifetime history of major depression or anxiety disorder and the sex difference begins in the early adolescence and persists through the mid-1950s.[1,2] It has been suggested that periods of hormonal variability, i.e., menarche,[3] premenstrual periods,[4] postpartum,[5,6] and perimenopause[7] increase the risk of mood disorders in certain women. Therefore it seems likely that sex steroid hormones can provide one possible explanation to the differences in mood disorders seen between genders. The central nervous system (CNS) is both a producer and target of sex steroids and three obvious examples where there seem to be evidence for the interaction between mood, steroids and CNS are the premenstrual dysphoric disorder (PMDD), side effects of oral contraceptives and negative mood symptoms encountered during sequential progestagen addition to estrogen treatment in postmenopausal women. Neuroendocrine factors such as neuroactive steroids are likely to contribute to the overall increased risk of developing mood disorders in women and in order to approach this vast problem a deeper understanding of the underlying mechanisms is most important.

One very obvious relation between sex steroids and mood symptoms are the symptoms related to the menstrual cycle. The sex hormones estradiol and progesterone display regular predictable changes during the menstrual cycle. In parallel with the progesterone increase an increase also occur in serum neuroactive steroids allopregnanolone (3α-OH-5α-pregnan-20-one) and pregnanolone (3α-OH-5β-pregnan-20-one).[8] Allopregnanolone, can be synthesized in the central nervous system but the major contributor to the concentration in the brain is the corpus luteum of the ovary.[9,10] Allopregnanolone and progesterone are produced in parallel during the luteal phase of the menstrual cycle.[8,11] 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.[12,13] Pregnanolone displays a similar luteal phase increase.[8,14] Allopregnanolon, pregnanolone and several other metabolites of steroid hormones are modulators of the Gamma Amino Butyric Acid-A ($GABA_A$) receptor and therefore called GABA-steroids.

20.2 Menstrual Cycle-Linked Mood Changes

The relation between the luteal phase of the menstrual cycle and symptom development in PMDD/PMS is obvious. The symptoms start at the time of ovulation and 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 day of menstruation. Thereafter the symptoms decline and disappear 3–4 days after the onset of menstrual bleeding. During the postmenstrual phase there is a period of well-being closely related to the estradiol peak.[15] This suggests that there is a symptom-provoking factor produced by the corpus luteum of the ovary. In anovulatory cycles, spontaneous or induced, when a corpus luteum is not formed and progesterone or allopregnanolone is not produced the symptom cyclicity disappears.[16–18] There is, however, a lag time of 4–5 days between peak of luteal steroids and peak of symptoms indicating that the symptom development takes some time to develop. This may be related to secondary gene transcriptional activity and subsequent protein synthesis due to enhanced $GABA_A$ receptor activation. This would eventually modulate the $GABA_A$ receptor composition and hence leading to the changes in GABA sensitivity occurring during the luteal phase.[8] The same mechanism occurs during tolerance development with change in the $GABA_A$ receptor subunit composition, which has been shown to occur during allopregnanolone treatment (see below).

The fact that progesterone and progestagens induce negative mood symptoms similar as in PMDD/PMS is shown in several studies, e.g., in postmenopausal women receiving estrogen/progesterone hormone replacement therapy[19–22] and in PMDD patients with induced anovulation.[23] Several types of progestagens are investigated and all seem to induce negative mood in certain sensitive individuals.[20,21,23]

20.3 Pathogenesis of Symptom Induction

The endocrine progesterone receptor is expressed in the brain and it is conceivable that some of progesterone's effects could be mediated via the classical endocrine progesterone receptor, resulting in changes in the $GABA_A$ receptor composition. However, the classical hormonal receptor for progesterone seems not to be involved in PMS/PMDD pathophysiology. Treatment with the endocrine progesterone receptor antagonist mifepristone (RU486) failed to reduce the physical or behavioral manifestations of PMS.[24]

Another possibility of importance for the pathogenesis of PMDD/PMS is related to the metabolism of progesterone, which is rapidly and to a high degree metabolized to allopregnanolone and pregnanolone in the liver, brain and other parts of the body.[25,26] Both steroids are acting as agonists on the $GABA_A$ receptor complex in the brain.[27] The GABA transmitter system is the major inhibitory system in CNS. When GABA binds to the $GABA_A$ receptor, the influx of chloride ions increases,

leading to a hyperpolarizing of the post-synaptic membrane, thus rendering the postsynaptic cell less prone to excitation. Allopregnanolone and pregnanolone are $GABA_A$ receptor positive modulators and enhances the effect of GABA on the receptor similar to ethanol, barbiturates, and benzodiazepins. Neurosteroids, benzodiazepines, barbiturates, alcohol and most anaesthetic agents bind to the $GABA_A$ receptor and increase the GABA-induced chloride ion influx by interacting with allosteric binding sites.[28]

20.4 Involvement of Positive $GABA_A$ Receptor Modulators in Mood Symptoms

Studies in animals and humans have reported typical $GABA_A$ receptor agonistic effects of high doses allopregnanolone and pregnanolone such as sedation/anaesthesia,[29,30] anti-epileptic effects,[31] and anxiolytic effects in animals.[32] However, reports from human and animal studies indicate that in certain individuals all $GABA_A$ receptor agonists also can induce negative symptoms with anxiety, irritability/aggressiveness. Strong irritability/aggression is induced in 3–6% of individuals and moderate symptoms are induced in 20–30%.[33,34] Interestingly, the prevalence of PMDD among women in reproductive age is in the similar range, 3–8%, of women in reproductive age and 25–35% have milder symptom severity as in PMS.[35]

Why an increase in allopregnanolone during the menstrual cycle is related to development of negative mood is puzzling as allopregnanolone should be anxiolytic like benzodiazepines. The answer seems to be the fact that all $GABA_A$ receptor agonists like benzodiazepines, barbiturates, alcohol and allopregnanolone have paradoxical anxiogenic effects in certain individuals. As mentioned above low concentrations or doses give severe adverse emotional reactions in a subset of individuals (3–6%) and moderate reactions in up to 20–30%. This paradoxical effect is induced by allopregnanolone[36,37] benzodiazepines,[38,39] barbiturates,[34,40,41] and ethanol.[37,42,43] The symptoms induced by these $GABA_A$ receptor active drugs are depressive mood, irritability, aggression and other symptoms known to occur during the luteal phase in women with PMS/PMDD. A bimodal effect has also been noted of different dosages of medroxyprogesterone (MPA) and natural progesterone in postmenopausal women taking hormone therapy (HT). These women feel worse on a lower dosage of MPA or progesterone than on a higher dosage or placebo.[22,44,45]

[Au1]

Thus allopregnanolone seem to have a bimodal effect on mood with an inverted U-shaped relationship between concentration and effect. In postmenopausal women receiving progesterone a biphasic relation between the negative mood symptoms and the allopregnanolone concentrations in blood is noted. The negative mood increases with the increase in serum concentration of allopregnanolone up to the maximum concentration seen during the luteal phase but with further increase in allopregnanolone concentration there is a decrease in symptom severity.[22,45] An inverted U-shaped relation between allopregnanolone dosage and irritability/aggression has also been noted in rats.[37]

Benzodiazepines also induce paradoxical reactions in certain individuals with irritability, aggression, depression, confusion, violent behavior and loss of impulse control compared to placebo.[38,46–48] The paradoxical effects of midazolam in patients who underwent surgery were effectively treated with flumazenil, a benzodiazepine receptor antagonist that effectively reversed the midazolam-induced paradoxical behaviours.[49] In rats the benzodiazepine-heightened aggressive behaviour induced by midazolam or triazolam was also antagonised by flumazenil and the $GABA_A$ receptor antagonists β-CCt and 3-PBC.[50,51]

20.5 FMRI and MRI Studies

The GABA turnover has been studied in PMDD patients and controls using magnetic resonance imaging (MRI) studies of occipital cortex and they indicate that the GABAergic system is substantially modulated during the menstrual cycle. PMDD patients and controls show different patterns in brain GABA concentration changes during the menstrual cycle suggesting that PMDD patients have a dysfunction in the GABA system.[52] During the menstrual cycle in control women there are significant changes in fMRI responses in adult human brain related to hormone variations but there are also region and task specific effects. (Fernández et al.[53]). FMRI studies can investigate the activity in defined brain areas during, e.g., emotional stimulation and under drug treatments. The amygdala is one part of the brain that is related to emotional experiences. Therefore it is interesting to study the responses to emotional stimulations during the menstrual cycle and when progesterone is given. Healthy women given progesterone show a modulation of amygdala reactivity to emotional stimuli. Progesterone administration increases the neural response to angry and fearful faces selectively in the amygdala compared to placebo at moderate progesterone and allopregnanolone plasma concentrations.[54] These results therefore show a neural mechanism by which progesterone could induce adverse effects on anxiety and mood. Because the acute effects of progesterone are likely mediated by allopregnanolone, this paradoxical amygdala activity increase might reflect the disinhibition of the principal neurons of the amygdala via inhibition of inhibitory interneurons. However, higher progesterone and allopregnanolone concentrations are associated with a decrease in amygdala reactivity during the intentional encoding of neutral and happy faces into memory.[54] Also benzodiazepines giving an anxiolytic response have been reported to decrease amygdala fMRI responses to angry and fearful face stimuli.[55] These fMRI results support the observation that allopregnanolone seems to induce negative mood changes in a nonlinear inverted U-shaped curve.[37,45,56] The increased amygdala response in the fMRI studies was observed when allopregnanolone levels had increased from the follicular phase range to the luteal phase or early pregnancy range.[8,57] The increased amygdala response might therefore be specific for this concentration change, and as shown in our study.[54] Supra-physiological concentrations seem to give another response as high doses of allopregnanolone injected into amygdala gives anxiolysis.[58]

20.6 PMDD/PMS Patients Have Different Sensitivity in the GABA-system

It seems thus as a subset of individuals are very sensitive to low doses or concentrations of allopregnanolone and respond with severe adverse emotional reactions when provoked. There is evidence that the sensitivity in the brain for steroids differs between PMS/PMDD patients and controls. Negative effects of oral contraceptives on mood were found mainly in women with PMS/PMDD and it was the lowest progestagen concentration that provoked symptoms.[59] Ad-back of estradiol or progesterone to women with PMS/PMDD and medically inhibited ovarian hormone production resulted in recurrence of symptoms. This relapse of symptoms did not occur in normal women or in PMS/PMDD women during placebo treatment.[23] Postmenopausal women with a history of PMS/PMDD responded with more negative symptoms on progestagens compared to women without a PMS/PMDD history.[21]

In PMS/PMDD patients but not in healthy controls the sedative response to intravenous pregnanolone, diazepam and alcohol is reduced in the luteal phase compared to follicular phase.[14,60–62] In addition, patients with severe symptoms were less sensitive to the given pregnanolone or benzodiazepines compared to patients with more moderate symptoms. These findings suggest that patients with PMS/PMDD develop tolerance for $GABA_A$ receptor allosteric agonists during the luteal phase. In an animal model of PMS/PMDD the allopregnanolone effect occurs in parallel with an up-regulation of the hippocampal alpha4 subunit of the $GABA_A$ receptor and decreased benzodiazepine sensitivity.[63] This is in line with the decreased benzodiazepine sensitivity in women with PMDD.[60] Especially animals with a high risk taking behavior develop withdrawal symptoms on progesterone treatment.[64]

Most $GABA_A$ receptor active substances will induce tolerance when used long term and this is also true for allopregnanolone. It has been shown that chronic administration of allopregnanolone will down regulate the $GABA_A$ receptor with a decreased GABA sensitivity of the $GABA_A$ receptor.[65] A tolerance to allopregnanolone is in rats noted already after 90 min of anesthesia.[66] Also, there is a relation between tolerance development and changes in the $GABA_A$ receptor subunit alpha4 in thalamus.[67] Tolerance to GABA-active neurosteroids might contribute to the symptoms in women with mood disorders and explain the decreased sensitivity to pregnanolone[14] benzodiazepines[60] and alcohol[62] seen in PMDD. A change in the $GABA_A$ receptor subunit composition has also been shown at allopregnanolone.[68] A withdrawal effect has also been suggested to induce negative mood when high levels of allopregnanolone in the luteal phase of the menstrual cycle suddenly decline.[68] The exact mechanisms and relation between tolerance developments, sensitivity to GABA-steroids and mood induction is not known but intense research is going on in the area to understand the pathogenesis of PMDD/PMS.

20.7 Role of Estradiol in Progesterone-Induced Mood Symptoms

Estradiol concentration is also of importance for the mood inducing effect of progesterone. Estradiol alone seems to be related to well-being in women with PMDD/PMS.[15] However, together with progesterone or progestagen the effect seems different. Higher estradiol dosage in postmenopausal hormone therapy (HT) during the progestagen period gave more severe symptoms compared to lower estradiol dosage in the same women but only during the period when the progestagen was given. During the period of unopposed estrogen no difference in mood severity was noted related to the estrogen dosage.[69] Similar results were seen in women with PMS/PMDD but not in controls with interrupted ovarian function as both estradiol and progesterone induced symptoms.[23] Increased estradiol and progesterone plasma levels during the luteal phase in patients with PMS are related to more severe symptoms compared to cycles in the same individuals with lower levels.[70] Moreover, estradiol treatment during the luteal phase induced more negative symptoms than placebo in PMS/PMDD patients.[71] Estradiol and progesterone acting together seem to induce another response in the central nervous system than when they act separately.

20.8 Conclusion

Ovarian steroid sex hormones and their metabolites are of fundamental importance for inducing negative mood in PMS/PMDD. We are starting to understand the mechanism in that the $GABA_A$ receptor sensitivity seems to be changed in women with PMS/PMDD and sensitive persons seem to react upon $GABA_A$ receptor agonists in a bimodal inverted U-shaped manner.

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