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The role of progesterone and GABA in PMS/PMDD

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TEMPORAL SYMPTOM – HORMONE RELATION

The relationship between the luteal phase of the menstrual cycle and symptom development in premenstrual dysphoric disorder/premenstrual syndrome (PMDD/PMS) is self-evident. Symptoms starts after ovulation and then increase in parallel with the rise in serum progesterone during the luteal phase. The symptom severity reaches a peak during the last five 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 following estrogen production, to the estradiol peak. This suggests that there is a symptom-provoking factor produced by the corpus luteum of the ovary.[1] This is further supported by the fact that in anovulatory cycles, spontaneous or induced, when a corpus luteum is not formed, no symptom cyclicity occurs.[2–4]

NATURE OF THE SYMPTOM-INDUCING FACTOR PRODUCED BY THE CORPUS LUTEUM OF THE OVARY

Further evidence that progesterone and progestogens induce negative mood symptoms similar to those in PMDD/PMS is seen in postmenopausal women receiving estrogen/progesterone hormone therapy.[5–7] As discussed above, there are strong indications that steroids from the corpus luteum are the symptom-provoking factor in the central nervous system (CNS). But the classical hormonal receptor for progesterone seems not to be involved in the patghophysiology of PMS/PMDD; treatment with the progesterone receptor antagonist mifepristone (RU-486) fails to reduce the physical or behavioral manifestations of PMS.[8]

THE DIRECT EFFECTS OF NEUROACTIVE PROGESTERONE METABOLITES ON THE GABA-A RECEPTOR

To understand progesterone-induced adverse mood effects, it is important to note that progesterone is to high degree metabolized to allopregnanolone (3α-OH-5α-pregnan-20-one) and pregnanolone (3α-OH-5β-pregnan-20-one), both of which act as agonists on the γ-aminobutyric acid A (GABA-A) receptor complex in the brain.[9] The GABA transmitter system is the major inhibitory system in the CNS. When GABA binds to the GABA-A receptor, the influx of chloride ions increases, hyperpolarizing the postsynaptic membrane and making the postsynaptic cell less prone to excitation. Allopregnanolone is a GABAA receptor positive modulator and enhances the effect of GABA on the receptor. The behavioral and pharmacological characteristics are similar to ethanol, barbiturates, and benzodiazepines. Neurosteroids, benzodiazepines, barbiturates, alcohol, and most anesthetic agents bind to the GABA-A receptor and increase the GABA-induced chloride ion influx by interacting with allosteric binding sites.[10,11]

NEUROACTIVE PROGESTERONE METABOLITES AS PMDD/PMS SYMPTOM-PROVOKING FACTOR

Thus far, studies have shown disparity regarding behavioral effects of these neuroactive progesterone metabolites. Studies in animals and humans have reported typical

GABA-A receptor agonistic effects such as sedation/anesthesia,[12,13] anti epileptic effects,[14] anxiolytic effects[15] of high doses of allopregnanolone and pregnanolone. Studies have also reported the negative effects of allopregnanolone, which has been shown to increase irritability/aggression[16] and inhibit learning.[17] Treatment with progesterone in a rat model of PMDD induces anxiety, related to an increased α_4 subunit of the GABA-A receptor in hippocampus, which in turn is attributed to an allopregnanolone effect.[18] Similar results, with a place aversion as a measure of anxiety in rats, were noted with a low dosage of allopregnanolone.[19]

Besides the neuroactive progesterone metabolites, benzodiazepines, barbiturates, and alcohol also act as positive modulators of the GABA-A receptor. Recent reports from human and animal studies indicate that in certain individuals all GABA-A receptor agonists can induce negative symptoms with anxiety and irritability/aggression. Strong irritability/aggression is induced in 3–6% of individuals; moderate symptoms are induced in 20–30%. Interestingly, the frequency parallels the 3–8% prevalence of PMDD among women in reproductive age and the 25–35% prevalence of milder symptoms, as in PMS.[20–22]

THE GABA ACTIVE AGONIST PARADOX

The GABA-A receptor agonists are known to be anxiolytic, sedative, and antiepileptic. Why an increase in allopregnanolone is related to development of negative mood is puzzling. It appears that benzodiazepines, barbiturates, alcohol, and allopregnanolone possess bimodal action on mood symptoms. In both animals and humans, GABA-A receptor agonists in high doses are anxiolytic, antiaggressive, sedative/anesthetic, and antiepileptic.[23,24] However, in low concentrations or doses, severe adverse emotional reactions are induced in a subset of individuals (2–3%) and moderate reactions in up to 20%. This paradoxical effect is induced by allopregnanolone,[16,19] benzodiazepines,[25,26] barbiturates,[20,27] and ethanol.[16,28] The symptoms induced by these GABA-A receptor active drugs include depressed mood, irritability, aggression, and other typical symptoms of PMS/PMDD. A similar bimodal effect has also been noted for different doses of medroxyprogesterone (MPA) and natural progesterone in postmenopausal women taking hormone replacement therapy (HRT). These women feel worse on a lower dosage of MPA or progesterone than they do on higher doses or placebo.[29,30]

Thus, allopregnanolone seem to have a bimodal effect on mood with an inverted U-shaped relationship between concentration and effect. In postmenopausal women receiving vaginal or oral progesterone, a biphasic relation between the negative mood symptoms and the allopregnanolone concentrations in blood is noted. Negative mood increases with the rise in serum concentration of allopregnanolone up to a maximum, but then further increase in allopregnanolone concentration is associated with a decrease in the severity.[5,31] The increase in negative mood occurs at serum concentrations within the range seen during the luteal phase. With concentrations seen during late pregnancy, the symptoms decrease.[32,33] In late pregnancy when allopregnanolone concentrations are at their highest, PMDD patients often feel better. A similar inverted U-shaped relationship between allopregnanolone dose and irritability/ aggression has also been noted in rats.[16]

Benzodiazepines also induce paradoxical reactions in certain individuals, with irritability, aggression, depression, confusion, violent behavior, and loss of impulse control compared with placebo.[25,26] Weinbroum et al reported a 10.2% incidence of paradoxical events to midazolam in patients who underwent surgery during a 3-month period and showed that the treatment with flumazenil (a benzodiazepine receptor antagonist) effectively reversed midazolam-induced paradoxical behavior.[22] Several reports from animal studies on benzodiazepine-heightened aggression show similar antagonistic effects of benzodiazepine antagonists, as seen in humans.[34]

ROLE OF ESTRADIOL IN PROGESTERONE-INDUCED MOOD SYMPTOMS

Estradiol concentration is also of importance in relation to the mood-inducing effect of progesterone. Higher estradiol doses in HRT during the progestogen period gave more severe symptoms compared with lower estradiol dosage in the same women but only during the period when the progestogen was given. During the period of unopposed estrogen, no difference in mood severity was noted in relation to the estrogen dose.[35] Similar results were seen in women with PMS/PMDD (but not controls) with, interrupted ovarian function where both estradiol and progesterone induced symptoms.[36] Increased plasma levels of estradiol and progesterone during the luteal phase in patients with PMS are related to more severe symptoms compared to cycles in the same individuals with lower levels.[37] Moreover, estradiol treatment during the luteal phase induced more negative symptoms than placebo in PMS/PMDD patients.[38] Estradiol and progesterone acting together seem to induce differing responses in the CNS than when they act separately.

SENSITIVITY IN THE GABA SYSTEM IN PMDD/PMS PATIENTS

It appears that a subset of individuals are very sensitive to low doses or concentrations of allopregnanolone and have severe adverse emotional reactions when provoked. There is evidence that steroid sensitivity in the brain differs between PMS/PMDD patients and controls. Negative effects of oral contraceptives on mood were found mainly in women with PMS/PMDD.[39] Add-back estradiol or progesterone, in women with PMS/PMDD and inhibited ovarian hormone production, gave rise to recurrence of symptoms. This did not happen either in normal women or in PMS/PMDD women during placebo treatment.[36] Postmenopausal women with a history of PMS/PMDD respond with more negative symptoms on progestogens than women without a PMS/PMDD history.[6] In PMS/PMDD patients but not controls, the sedative response to intravenous pregnanolone, diazepam, and alcohol is reduced in the luteal phase compared with the follicular phase.[40–42] In addition, patients with severe symptoms were less sensitive to the given pregnanolone or benzodiazepines compared to patients with more moderate symptoms.[36,38] The findings suggest that patients with PMS/PMDD develop tolerance to the administration of GABA-A receptor allosteric agonists during the luteal phase. In an animal model of PMS/PMDD, the allopregnanolone effect occurs in parallel with an upregulation of the hippocampal α_4 subunit of the GABA-A receptor and decreased benzodiazepine sensitivity.[18] This is in line with the decreased benzodiazepine sensitivity in women with PMDD.[41] Animals with high risk-taking behavior develop withdrawal symptoms on progesterone treatment.[43] The decreased sensitivity is an indication of the development of tolerance to allopregnanolone. Tolerance to allopregnanolone in rats after 90 minutes of anesthesia has already been noted.[44] There is also a relationship between tolerance development and change in the GABA-A receptor subunit α_4 in thalamus.[45]

CONCLUSION

In conclusion, ovarian steroid hormones are of fundamental importance in inducing negative mood in PMS/PMDD. We are beginning to develop an understanding of a mechanism where GABAA receptor sensitivity seems to differ in women with PMS/PMDD and sensitive individuals appear to react to GABAA receptor agonists in a bimodal inverted U-shaped manner.

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