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Effects of GABA active steroids in the female brain with a focus on the premenstrual dysphoric disorder

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Abstract

Premenstrual dysphoric disorder (PMDD) afflicts 3%-5% of women of childbearing age, and is characterised by recurrent negative mood symptoms (eg, irritability, depression, anxiety and emotional lability) during the luteal phase of the menstrual cycle. The aetiology of PMDD is unknown, although a temporal association with circulating ovarian steroids, in particular progesterone and its metabolite allopregnanolone, has been established during the luteal phase. Allopregnanolone is a positive modulator of the GABA_A receptor: it is sedative in high concentrations but may precipitate paradoxical adverse effects on mood at levels corresponding to luteal phase concentrations in susceptible women. Saccadic eye velocity (SEV) is a measure of GABA_A receptor sensitivity; in experimental studies of healthy women, i.v. allopregnanolone decreases SEV. Women with PMDD display an altered sensitivity to an i.v. injection of allopregnanolone compared to healthy controls in this model. In functional magnetic resonance imaging (fMRI) studies, women with PMDD react differently to emotional stimuli in contrast to controls. A consistent finding in PMDD patients is increased amygdala reactivity during the luteal phase. Post-mortem studies in humans have revealed that allopregnanolone concentrations vary across different brain regions, although mean levels in the brain also reflect variations in peripheral serum concentrations. The amygdala processes emotions such as anxiety and aggression. This is interesting because allopregnanolone is detected at high concentrations within the region into which marked increases in blood flow are measured with fMRI following progesterone/allopregnanolone administration. Allopregnanolone effects are antagonised by its isomer isoallopregnanolone (UC1010), which significantly reduces negative mood symptoms in women with PMDD when administered s.c. in the premenstrual phase. This was shown in a randomised, placebo-controlled clinical trial in which the primary outcome was change in symptom scoring on the Daily Rating of Severity of Problems (DRSP): the treatment reduced negative mood scores ($P < .005$), as well as total DRSP scores ($P < .01$), compared to placebo in women with PMDD. In conclusion, the underlying studies of this review provide evidence that allopregnanolone is the provoking factor behind the negative mood symptoms in PMDD and that isoallopregnanolone could ameliorate the symptoms as a result of its ability to antagonise the allopregnanolone effect on the GABA_A receptor.

KEYWORDS

GABA, neuroactive steroids, premenstrual dysphoric disorder

1 | INTRODUCTION

Allopregnanolone (3 α -OH-5 α -pregnan-20-one) is one of several endogenous progesterone metabolites that, unlike progesterone, is a potent positive modulator on the GABA_A receptor in the brain.¹ Progesterone itself shows classical actions via nuclear progesterone receptors (PRs) that, as a result of ligand binding, activate gene expression via progesterone response elements, as well as actions via nonclassical signalling pathways. Nonclassical actions are generally rapid and include activation of membrane-bound PR, cytoplasmic PR or receptor-independent intracellular signalling cascades.² Allopregnanolone is produced from progesterone by the succeeding actions of the enzymes 5 α -reductase type I and 3 α -hydroxysteroid dehydrogenase. These two enzymes are not homogeneously expressed in the brain, although they are highly expressed and colocalised in, for example, specific neurones in the cerebral cortex, hippocampus and amygdala.³

The GABA system is the main inhibitory transmitter system in the brain. The GABA_A receptor is membrane bound and consists of five subunits, forming a chloride channel. At least 19 different subunits have been identified so far, making numerous combinations possible.⁴ GABA_A receptors are ubiquitously distributed within the brain and are located both synaptically (mediating phasic inhibition) and extrasynaptically (effecting tonic inhibition).⁵ The subunit composition of GABA_A receptors varies in a site-specific manner throughout the different areas of the brain,⁶ and different GABA_A receptor subtypes exert differing pharmacological responses.^{4,7,8} Allopregnanolone acts as a positive allosteric modulator on the GABA_A receptor in the lower concentration range but, at high concentrations, it can activate the receptor directly without the presence of GABA.⁹ GABA_A receptor potentiating neurosteroids, such as allopregnanolone, bind to the receptor at a specific binding site located at the α - and β -subunits interface, near the lipid interface, for both activation and potentiation of the receptor.¹⁰ In vivo, high concentrations of allopregnanolone, as well as other GABA_A receptor agonists, such as benzodiazepines and barbiturates, have revealed anaesthetic and anti-epileptic properties in both animals and humans.¹¹⁻¹⁴ In addition, allopregnanolone has been shown to mediate anxiolytic effects in animal experiments.¹⁵ In women, peripheral levels of allopregnanolone mirror fluctuations of progesterone across the menstrual cycle and during pregnancy,^{16,17} and variations in concentration are also noted within the brain.¹⁸ One of several possible physiological roles of endogenous allopregnanolone is to act as a neuroprotective agent contributing to a normal development of the foetal brain during pregnancy.^{19,20} Nevertheless, allopregnanolone is also likely involved in pathological conditions such as the premenstrual dysphoric disorder (PMDD).

2 | PMDD

Approximately 3%-5% of women of childbearing age suffer from PMDD, a condition typified by mental symptoms such as irritability, depressed mood, aggression and emotional lability that all consistently

recur in the premenstrual phase of the menstrual cycle.^{21,22} The pathophysiology of PMDD is unclear, although a temporal association with circulating ovarian steroids, in particular progesterone and its metabolite allopregnanolone, has been established.²³ A prerequisite for PMDD symptoms is that menstrual cycles are ovulatory. In women with PMDD, negative mood symptoms are abolished in spontaneously anovulatory cycles, as well as during treatment with gonadotrophin-releasing hormone (GnRH) analogues.^{24,25} Although PMDD shares symptomatology with several psychiatric conditions (eg, endogenous depression and generalised anxiety disorder), it is not considered to be a variant of these conditions, and is defined as a particular entity in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5). The DSM-5 criteria state that women with PMDD should be free of symptoms during the postmenstrual week, whereas symptoms present in the premenstrual week should be severe and have a significant impact on daily activities, relationships, work performance and social functioning.²⁶ Furthermore, a PMDD diagnosis should be based on at least 2 months of prospective daily symptom ratings, preferably on a validated scale such as the Daily Record of Severity of Problems (DRSP).²⁷ Comorbidity with other affective disorders (eg seasonal depression) and anxiety disorders is common,^{28,29} and earlier trauma appears to be a significant risk factor for PMDD.³⁰ PMDD criteria according to the DSM-5 are stringent and it has been estimated that the proportion of women in need of treatment for premenstrual dysphoria is much larger than those who fulfil the current criteria.^{22,31} Apart from ruling out ongoing psychiatric conditions, which require special attention from a psychiatrist, prospective symptom scorings are useful with respect to educating patients about PMDD. The pattern of symptoms rated by women with PMDD is clearly distinguishable from the pattern rated by women without symptom cyclicity. The time period in the luteal phase, during which symptoms are disturbing, could vary between a few days up to 2 weeks but, usually, symptoms start to occur after ovulation around day 14 in the menstrual cycle (Figure 1).³²

3 | TREATMENT OF PMDD

Today, first-line treatment for PMDD is a selective serotonin receptor inhibitor (SSRI) administered using an intermittent dosing regimen during the luteal phase.^{33,34} Symptom cyclicity in women with PMDD is characterised by a large inter-individual variability, although it usually exhibits a low intra-individual variability: as a result, the number of necessary treatment-days is highly variable between women. An effective strategy could even be to start treatment at onset of symptoms.³⁵ SSRI side-effects, especially with regard to sexual function, are common, and it is therefore critical to minimise exposure to the drug, at the same time ascertaining a sufficient treatment effect. Nevertheless, compliance is poor and many women terminate treatment on account of bothersome adverse effects.³⁶

Because PMDD symptoms are absent in anovulatory cycles, combined oral contraceptives (COC) present an alternative for treatment. Combinations with drospirenone especially have been proven to be more effective than placebo in randomised controlled trials.^{37,38}

However, the risk for adverse mood effects as a result of the synthetic hormones persists; in a general population of women, combined oral contraceptives have been shown to aggravate mood symptoms.³⁹

FIGURE 1 Comparison between premenstrual dysphoric disorder (PMDD) patients (n = 18) and controls (n = 20) with regard to self-rated PMDD symptoms during two menstrual cycles (mean $\pm$ SEM). Menstruation starts at menstrual cycle day 1 and ovulation occurs around day 14. Reproduced by permission³²

In severe cases of PMDD, treatment with GnRH analogues is an option. However, as a consequence of the bone demineralisation effects of hypoestrogenic states, “add-back” therapies using a combination of oestrogen and progestogen are necessary. The dosage and combination of add-back hormone therapy must be carefully considered with regard to impact on mood; some women are exquisitely sensitive to exogenous hormone administration, particularly to progestogens.⁴⁰ Oophorectomy may be considered in the most severe cases, although problems associated with attaining optimal add-back therapies remain.⁴¹

4 | EFFECTS OF ALLOPREGNANOLONE

Human post-mortem studies have revealed that peripheral levels of progesterone and allopregnanolone are reflected in the brain and correlate with the endocrine state at time of death (Figure 2). Peripheral serum levels of progesterone correlated with brain tissue concentrations of progesterone in most of the brain areas sampled ($P < .05$). Furthermore, variations in allopregnanolone brain distribution have been uncovered, with especially high concentrations detected in the amygdala (Figure 3), indicating that differences in progesterone metabolism may be presented locally in brain tissue.¹⁸ Allopregnanolone is a positive modulator of the GABA_A receptor and causes both sedation, at high concentrations, and paradoxical reactions with adverse mood in susceptible women.⁴² However, simple relationships (such as an excess or deficiency of allopregnanolone in women with PMDD) have not been established in systematic studies.⁴³ Nevertheless, in women with PMDD, premenstrual mood improves when serum levels of allopregnanolone are decreased, either by inhibiting ovarian progesterone production or by diminishing progesterone metabolism using a 5 α reductase inhibitor.^{44,45} Further evidence that progesterone is probably not directly involved in the pathogenesis of PMDD

FIGURE 2 Postmortem brain concentrations of progesterone, 5 α -pregnane-3,20-dione (5 α -DHP) and 3 α -hydroxy-5 α -pregnanolone (3 α -OH-5 α -pregnanolone; allopregnanolone) in women with high serum progesterone concentrations (white bars) compared to women with low serum progesterone concentrations (black bars). Mean $\pm$ SEM tissue concentration based on samples from frontal, temporal, parietal and cingulate cortex, amygdala, hippocampus, caudate nucleus, putamen, thalamus, nucleus accumbens, hypothalamus (medial and basal hypothalamus and preoptic area), substantia nigra, pons, cerebellum and medulla oblongata are presented. Differences between the two groups were tested with a two-way ANOVA. Reproduced with permission¹⁸

is that treatment with mifepristone, a progesterone receptor antagonist, fails to ameliorate mood symptoms.⁴⁶ Similar to other GABA_A receptor agonists (eg, benzodiazepines and barbiturates), allopregnanolone may induce tolerance and this has been demonstrated in animal studies.⁴⁷ The effects of allopregnanolone could be studied experimentally in humans using other techniques: for example, acute effects of GABA-ergic substances on saccadic eye velocity have been studied earlier, as well as effects on emotional circuits using brain-imaging techniques. These methods are described more in detail below.

5 | SACCADIC EYE VELOCITY

Measurement of saccadic eye velocity (SEV) by electrooculography is an established method for detecting GABA_A-mediated sedation.⁴⁸ During a test session, the induced potential, during which the vector over the ophthalmic bulb is changed by the quick movement of the eye (the saccade) to focus the fovea on an array of individually lighted diodes, is registered. The diodes are lighted one at a time and the subject is asked to focus on, and follow, the lighted dots projected on a wall in front of them without anticipating the target. Appropriate software is used to analyse and calculate the saccadic eye velocity. Saccadic eye velocity reaches a maximum at 30–35° of angular movement; maximum velocity at 30° is a common outcome measurement. SEV is indirectly proportional to GABA_A receptor activity and the saccade cannot be controlled by motivational influence once it has begun.⁴⁸ The method is stable and sensitive to the influence of substances modulating GABA_A receptor activity. Although SEV varies

greatly between individuals, it has high intra-individual stability across repeated trials.⁴⁹

Measurement of SEV can thus be used to quantify GABA_A receptor sensitivity⁵⁰ and, in experimental studies of healthy women, i.v. allopregnanolone dose-dependently increases sedation and decreases maximal SEV.¹¹ In a study by our research group, women with PMDD were shown to have an altered sensitivity to an i.v. injection of allopregnanolone compared to healthy controls. PMDD women were more sensitive during the luteal phase as opposed to during the follicular phase, whereas the reverse was seen in healthy controls (Figure 4). The conclusion from these results was that women with PMDD might not be able to develop a physiological tolerance to allopregnanolone during the luteal phase.⁵¹

6 | FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) STUDIES

fMRI constitutes an important tool for exploring the workings of the brain in the context of psychiatric and neurological disorders. A majority of studies have focused on localising brain foci underlying deficits in cognitive, affective and social information processing, as a function of increases or decreases in blood-oxygenation-level-dependent (BOLD) signal levels in the setting of carefully designed experimental manipulations.⁵² In an attempt to unravel the functional aberrations underlying PMDD, the focus of studies has been on dysfunctional activity in a number of key structures: most notably the amygdala, which has emerged as a crucial component of networks involved in the modulation of attention and vigilance to emotionally salient

FIGURE 3 Concentrations of progesterone, 5α-pregnane-3,20-dione (5α-DHP) and 3α-hydroxy-5α-pregnane-20-one (3α-OH-5α-pregnanolone; allopregnanolone) in specific regions of the human female brain. Allopregnanolone levels were significantly higher in the amygdala than in the other brain areas, apart from the hypothalamus and substantia nigra (not shown in the figure), $P < .05$, one-way ANOVA. FC, frontal cortex; TC, temporal cortex; PC, parietal cortex; AM, amygdala; HI, hippocampus; CN, caudate nucleus; PU, putamen; TH, thalamus. Reproduced with permission¹⁸

information,⁵³ and is commonly found to be hyperactive in a number of anxiety disorders such as post-traumatic stress disorder and social phobia.⁵⁴ Nonetheless, the current trend is to move away from trying to pin down functional abnormalities to individual brain areas and, instead, to focus on trying to understand how distributed foci operating in large-scale networks contribute to psychopathology.⁵² The most recent hypothesis underlying affective dysregulation in PMDD suggests that exaggerated bottom-up activation of the salience network, coupled with blunted top-down regulation by fronto-cingulate regions, and dysregulated functional coupling between the salience and executive control network, lies at the basis of the affective symptomatology in PMDD.⁵⁵

Thus far, the most reliable finding in studies investigating menstrual cycle-linked differences in functional brain activity is that women with PMDD exhibit a higher reactivity in the amygdala during the luteal phase compared to asymptomatic controls.^{56,57} In turn, increased amygdala reactivity during the luteal phase, in contrast to the follicular phase, has been reported in healthy naturally cycling women in response to negatively valenced pictures during facial expression discrimination tasks and when recalling negative emotionally arousing information.^{58–60} In women with PMDD, increased amygdala and insula reactivity to negative social stimuli in the luteal phase was coupled with lower reactivity in the anterior cingulate cortex, and changes in reactivity were correlated with rising progesterone levels.⁵⁷ On the other hand, PMDD patients exhibit lower phase-independent emotion-induced activity in the pre-genual anterior cingulate and ventromedial prefrontal cortex compared to controls.⁶¹ Exogenous administration of progesterone to healthy women in the early follicular phase, along with a subsequent increase in allopregnanolone levels, has been shown to selectively increase amygdala reactivity in response to facial stimuli.⁶²

Furthermore, low concentrations of progesterone/allopregnanolone increased the activity in the amygdala, whereas high concentrations decreased activity. A similar phenomenon is observed in association with the anxiolytic effect of benzodiazepines, whereby a reduction in anxious feelings is accompanied by a decrease in amygdala reactivity. Similarly, exogenous progesterone has shown to decrease memory performance, in correspondence with a reduced reactivity in the amygdala and some other brain regions.⁶³ The field of neuroimaging in PMDD is still in its infancy, although the few studies published thus far have already yielded interesting findings, indicating that fMRI might be a useful tool for studies of the pathophysiology of PMDD.

7 | GABA_A RECEPTOR FUNCTION

The plasticity of the GABA_A receptor may vary with reproductive state, as in the rat brain where the expression of δ subunits is associated with physiological variations of ovarian hormones during the oestrus cycle,^{64,65} a change which is most likely mediated by allopregnanolone.⁶⁶ δ Subunits are present in extrasynaptic GABA_A receptors, and confer upon them an increased sensitivity to allopregnanolone.⁶⁷ Also, the cell surface expression of extrasynaptic $\alpha 4$ -subunit containing GABA_A receptors can be increased by allopregnanolone with a concomitant increase in tonic current.⁶⁸ In a mouse model, allopregnanolone increased anxiety-driven behaviour under conditions where $\alpha 4\delta$ subunits were up-regulated in the hippocampus, an effect that was absent in $\alpha 4$ or δ knockout animals.^{69,70} Based on these findings, a reasonable assumption is that the altered response to allopregnanolone in women with PMDD may be related to the plasticity of the GABA_A receptor.

FIGURE 4 Area under the curve for saccadic eye velocity (SEV) change from baseline (mean $\pm$ SEM Δ deg s⁻¹) after an i.v. injection of allopregnanolone (0.05 mg kg⁻¹), once in the follicular and once in the luteal phase, in women with premenstrual dysphoric disorder (PMDD) and healthy controls. PMDD women were more sensitive to allopregnanolone in the luteal compared to the follicular phase, * $P < .05$ (Wilcoxon signed rank test). Reproduced with permission⁵¹

FIGURE 5 Area under the curve for saccadic eye velocity (SEV) change from baseline (mean $\pm$ SEM Δ deg s⁻¹) following i.v. administration of allopregnanolone (AP) (0.05–0.07 mg kg⁻¹), AP + isoallopregnanolone (ISO) (0.05 mg kg⁻¹ and 0.07 mg kg⁻¹) or AP:ISO (0.05 mg kg⁻¹ and 0.13 mg kg⁻¹). The decrease in SEV was significantly smaller when AP was administered together with ISO compared to AP alone. * $P < .05$ (Wilcoxon signed rank test). Reproduced with permission⁷⁴

FIGURE 6 Significant reduction of total Daily Rating of Severity of Problems (DRSP) score (top), negative mood score (middle) and impairment (bottom) in women with pure PMDD treated with UC1010 compared to placebo during the symptomatic luteal phase ($n = 60$). Mean $\pm$ SEM reduction in ratings and change in scores from baseline (percentage change) are shown. Group differences tested with the Mann-Whitney test. Reproduced with permission⁸⁵

8 | ISOALLOPREGNANOLONE

In vitro and animal studies have highlighted the presumed non-competitive antagonistic effect of the endogenous steroid isoallopregnanolone (3β -OH- 5α -pregnan-20-one) on its isomer allopregnanolone.⁷¹⁻⁷³ In humans, this antagonistic relationship has been illustrated using the SEV model; indeed, studies have shown that allopregnanolone-mediated sedation is antagonised non-competitively by a simultaneous injection of isoallopregnanolone (allopregnanolone 0.05 mg kg^{-1} and isoallopregnanolone 0.07 or 0.12 mg kg^{-1}) (Figure 5).⁷⁴ Serum levels of endogenous isoallopregnanolone fluctuate in concert with progesterone and allopregnanolone concentrations and exhibit corresponding variability

depending on the reproductive state.⁷⁵⁻⁷⁷ During pregnancy, levels of isoallopregnanolone increase in parallel with allopregnanolone with a constant ratio of approximately 1:4 of the serum concentration and, during the menstrual cycle, the ratio is 1:4 to 1:2.⁷⁸ In humans, it is obvious that some of i.v. injected isoallopregnanolone is converted to allopregnanolone and also that some of i.v. injected allopregnanolone is converted to isoallopregnanolone.^{74,79} Isoallopregnanolone can be produced from allopregnanolone either in a two-step reaction with dihydroprogesterone produced as an intermediate or by direct epimerisation.^{80,81} The enzymes responsible for these conversions are present within the brain, although most are abundantly found within the liver. The physiological role of isoallopregnanolone is at present unknown; in early studies of neuroactive steroids, the compound was even used as an inert control.⁸² Isoallopregnanolone has no effects of its own on the GABA_A receptor in vitro⁸³ and does not directly antagonise GABA action.⁷¹ Moreover, the antagonistic effect of isoallopregnanolone on allopregnanolone modulation of GABA_A receptor function appears to be specific because it does not influence the effect of other GABA_A receptor agonists such as benzodiazepines or barbiturates or GABA itself.^{71,84}

9 | ISOALLOPREGNANOLONE AS TREATMENT FOR PMDD

In a first, proof-of-concept trial, isoallopregnanolone (UC1010) was tested against placebo as a potential novel treatment modality for PMDD. This multicentre study comprised a phase II parallel group trial including women with PMDD as specified by DSM-5. Participants were screened using the DRSP scale prior to inclusion and the DRSP was also used for outcome measurement after 1 month of treatment. Active drug (UC1010) and placebo were administered as s.c. injections, repeatedly during the luteal phase and treatment was double-blinded. No severe side effects were reported and the results are shown in Figure 6.⁸⁵ The primary outcome was a change in symptom scoring on the DRSP. The treatment effect was significantly superior to placebo in the 60 women with pure PMDD: the treatment reduced negative mood scores ($P < .005$), as well as total DRSP scores ($P < .01$). Moreover, the effect size proved to be similar to that obtained in other treatment studies with SSRIs or COCs in women with PMDD, using the same outcome measures.^{37,86,87} Considering its safety and proven effect in this first study, UC1010 represents a promising future treatment for PMDD.

10 | CONCLUSIONS

Women with PMDD have an altered sensitivity to the progesterone metabolite allopregnanolone, which is a positive modulator acting on the GABA_A receptor. The effect could be antagonised by isoallopregnanolone in vitro, in animal models and in humans, and thus constitutes a possible future treatment for PMDD.

CONFLICT OF INTERESTS

Torbjörn Bäckström have shares in Asarina Pharma who sponsored the clinical trial with UC1010. None of the other authors have any conflicts of interest.

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