Neuroactive Steroids and Depression

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Case Vignette

Ms. A is a 64-year-old woman who has been struggling with depression since her 30s. She was diagnosed with severe major depressive disorder (MDD) 3 months ago. Despite a trial of an SSRI at an adequate antidepressant dose for more than 2 months, she remains significantly depressed, with a MADRS score in the moderate depression range. The depression is so severe that she is having difficulty maintaining relationships and a career, and at times, she has found it difficult to venture outside of her house. She has been offered a number of augmentation therapy options, including an atypical antipsychotic, but she is worried about the potential side effects and therefore has declined. She decided to enroll in an 8-week, open-label pilot study of ganaxolone (Marinus Pharmaceuticals), an oral neuroactive steroid analog, for treatment-resistant depression. At the end of the 8-week trial, Ms. A reported minimal residual depression, though she did note side effects of increased tiredness and some dizziness. Because no placebo-controlled trials have been conducted, it is unknown whether this neuroactive steroid analog is effective for the treatment of treatment-resistant depression or whether Ms. A experienced a placebo effect.

What Are Neuroactive Steroids?

Steroid hormones are derivatives of cholesterol that are synthesized by the ovaries, testes, and adrenal glands. Certain metabolites of these hormones, formed after enzymatic conversion, can travel to the brain and act at receptors that are known to modulate affective and neurologic disorders. Majewska et al. made the seminal observation in *Science* in 1986 that metabolites of progesterone and deoxycorticosterone increase gamma-aminobutyric acid (GABA) – a potent central nervous system inhibitory neurotransmitter – inhibitory activity in rat hippocampal and spinal cord neuron cultures [1]. The most well-studied neuroactive steroids are metabolites of progesterone. Of the progesterone metabolites, much interest has been focused on allopregnanolone, which is converted from progesterone in a two-step process, by the enzymes 5α-reductase and 3α-hydroxysteroid dehydrogenase (3α-HSD) [2, 3] (Fig. 11.1). Allopregnanolone is a positive allosteric modulator at $GABA_A$ receptors where benzodiazepines act. However, allopregnanolone's potency is about 10 times that of benzodiazepines at these receptors [1, 2, 4], raising the possibility that it might play a role in affective, anxious, and other psychiatric disorders and could be an effective therapeutic target.

What Is the Evidence that Neuroactive Steroids May Play a Role in Depression?

There are several lines of evidence that support a role for neuroactive steroids in depression. For example, there are a few, small cross-sectional studies that have demonstrated inverse associations between allopregnanolone levels and severity of depression symptoms. These include studies in women with MDD in which mean cerebrospinal fluid (CSF) [5] and serum levels of allopregnanolone have been generally lower than in controls without MDD [6, 7].

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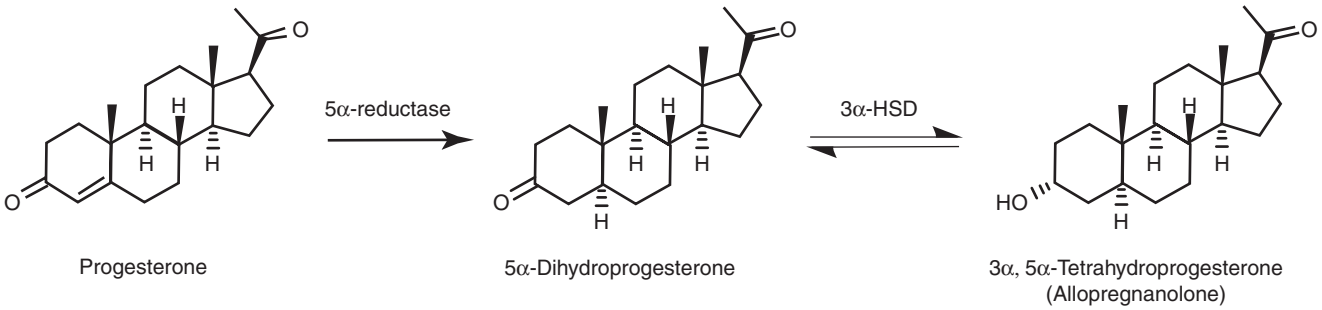

Fig. 11.1 Progesterone is converted to the neuroactive steroid allopregnanolone through enzymatic conversion [8]. (Modified from Dichtel et al. [8])

Moreover, we have recently reported that serum levels of allopregnanolone are inversely associated with depression symptom severity across the weight spectrum in women with anorexia nervosa, normal controls, and women with obesity. Both anorexia nervosa and obesity are complicated by a high prevalence of comorbid depression. We therefore hypothesized that serum allopregnanolone levels would be relatively lower in women with anorexia nervosa and inversely associated with depression symptom severity throughout the weight spectrum, independent of weight. We studied 36 women, 12 with anorexia nervosa, 12 healthy controls, and 12 with obesity. The three groups were age-matched, and none were receiving antidepressants or other psychotropic medications. All of the women with anorexia nervosa were amenorrheic, and all healthy lean controls and women with obesity had regular menstrual cycles and were studied during the follicular phase of the menstrual cycle in the morning and fasting. Allopregnanolone and progesterone levels were measured using the gold standard method, gas chromatography/mass spectrometry. As expected, the anorexia nervosa group had the highest mean depression and anxiety symptom severity scores ($p < 0.0001$). Although the overweight/obesity group had no history of diagnosed depression or anxiety, mean depression and anxiety severity scores were higher than in the healthy, lean controls. In concert with the higher depression and anxiety scores in these two groups, we found that serum allopregnanolone levels were on average lowest in the women with anorexia nervosa, intermediate in the overweight/obesity group, and highest in the lean control group ($p < 0.01$). This relationship was independent of precursor (progesterone) levels. In addition, allopregnanolone, but not progesterone, levels were inversely associated with depression and anxiety symptom severity, such that women with the lowest allopregnanolone levels generally had more severe depression and anxiety. This was true within the group as a whole and within the group of women with anorexia nervosa. These relationships were independent of participant weight and of progesterone levels. The importance of the last point is that it suggests we are not simply measuring variability of ovarian-derived neuroactive steroid precursor hormone levels but rather differential regulation of the metabolism of these hormones that may be important regulators of mood [8].

In addition, there are studies that demonstrate an increase in allopregnanolone levels in CSF and blood with selective serotonin reuptake inhibitors (SSRIs), which have led some investigators to hypothesize that an increase in neuroactive steroids may be one mechanism by which SSRIs reduce depression severity [5, 7, 9, 10]. Uzunova et al. measured CSF ALLO levels (allopregnanolone plus its isomer) in 15 patients with unipolar major depression before and after SSRI administration. They reported that levels in depressed patients were approximately 60% lower than in normal controls and normalized following SSRI treatment. Moreover, the degree of increase in CSF ALLO levels was significantly associated with the reduction in depression symptom severity [5]. Further, Romeo et al. demonstrated increases in serum levels of allopregnanolone and its isomer with SSRI treatment [9]. These studies suggest that neuroactive steroid levels may be relatively low in at least some patients with depression and that SSRI therapy may augment such levels. However, in another study, Strohle et al. reported that serum allopregnanolone levels increased with antidepressant administration in nine depressed subjects [7]. In that study, several different classes of antidepressants were used – none of which were SSRIs or related medications. Therefore, further investigations are needed to determine whether the increases in neuroactive steroid levels observed in such studies provide clues to mechanisms responsible for SSRI effects or are simply a reflection of the improvement in depression and/or anxiety symptom severity observed in itself. However, a direct effect of SSRIs is possible, and a study by Griffin et al. provided data supporting a specific mechanism by which SSRIs may increase allopregnanolone levels [11]. They demonstrated that fluoxetine, paroxetine, and sertraline, but not imipramine, decreased the Km of the last enzymatic conversion in the pathway from progesterone to allopregnanolone in human fetal brain cells [11], suggesting a possible mechanism responsible for allopregnanolone increase by SSRI administration. Therefore, further investigations in this area are warranted.

Research: Effects of Neuroactive Therapies in Patients with Depression

Research in this area is being pursued by pharmaceutical companies, which had originally developed allopregnanolone preparations and analogs to treat epilepsy refractory to standard medical approaches, as well as by individual academic investigators. In recent promising but preliminary studies, allopregnanolone administration has been shown to exert antidepressant effects in women with postpartum depression. A double-blind, phase 2, randomized, placebo-controlled trial of 21 in patients with severe depression [12] confirmed a previous open-label trial showing antidepressant efficacy [13]. Allopregnanolone, in the form of brexanolone (Sage Therapeutics), an intravenous formation that is infused continuously for 60 h, was administered, resulting in a marked reduction in depression symptom severity (mean 21 points on the HAM-D) [12]. No adverse events serious enough to cause study discontinuation occurred [12]. These initial, small trials are promising. This therapy is not FDA-approved, and further studies are ongoing.

In December, 2017, in a press release, Sage Therapeutics provided a preview of positive results of a phase 2, placebo-controlled study of an oral investigational medication, SAGE-217, a positive allosteric $GABA_A$ modulator for the treatment of MDD. In the study, 89 patients with moderate to severe MDD were randomized to receive the medication or placebo for 14 days, with a significant reduction in depression symptom severity as measured by the Hamilton Rating Scale for Depression [14]. Furthermore, we have recently completed an open-label pilot study investigating the effects of ganaxolone on depression symptom severity in postmenopausal women with treatment-resistant depression (results pending), which, if positive, could form the foundation for future, controlled studies.

Although most research in this area has focused on allopregnanolone and allopregnanolone analogs, there is also a small literature on pregnenolone, which is a steroid hormone with neuroactive properties. Pregnenolone is enzymatically converted from cholesterol and is a precursor to progesterone. It is available as a dietary supplement and can be prepared by compounding pharmacies. Brown et al. randomized 80 adults with bipolar depression to receive add-on therapy in the form of pregnenolone 500 mg daily and reported a decrease in depression symptom severity, as measured by the Hamilton Rating Scale for Depression, but not the Inventory of Depression Severity-Self-Report, without an increase in manic symptoms [15]. Allopregnanolone levels increased in subjects receiving pregnenolone [15], and other studies have shown that pregnenolone administration results in increases in progesterone levels [16], raising the question of which neurosteroid(s) to which to attribute the improvements in depression severity observed.

Role of Neuroactive Steroids in Patients in Other Psychiatric Disorders

The potential role of neuroactive steroids in other psychiatric disorders, including anxiety disorders [17], is also an area of investigation but beyond the scope of this review. Given the luteal phase timing of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), an etiopathologic role for progesterone metabolites is an attractive hypothesis, and allopregnanolone levels have been examined in a few studies in women with PMS. There is some evidence of a relative deficiency in a study using HPLC to separate allopregnanolone from its precursor hormones [18], whereas studies using immunoassays have been contradictory [19, 20]. More research in this area may provide interesting insights.

Extensive studies of the role of neuroactive steroids in post-traumatic stress disorder (PTSD) have also been published. CSF levels of ALLO in women with the disorder are 60% lower than in healthy controls, and ALLO/DHEA levels are inversely associated with negative mood symptoms [21]. Because study participants had normal levels of the allopregnanolone precursor, 5α-dihydroprogesterone, and a high 5α-dihydroprogesterone/ALLO ratio, the authors concluded that the relatively lower CSF ALLO levels in such subjects were either due to lower 3α-HSD expression or activity or higher metabolism of ALLO than in health controls. This study led to interest in developing neuroactive steroid treatments for PTSD. However, the first such study – a multisite, double-blind, placebo-controlled trial of ganaxolone (Marinus Pharmaceuticals), an oral allopregnanolone analog – did not demonstrate a significantly greater effect of the medication compared with placebo on PTSD symptoms, quality of life, or mood [22]. Whether the findings of this study can be generalized or whether compliance, the large placebo effect, or other factors related to the specific participants studied or the specific drug administered were the cause of these negative results is unclear.

Challenges to Further Research in This Area

A major challenge to further research in this area is the great degree of homology between different, related, neuroactive metabolites of the same hormone and between the neuroactive metabolites and their precursor hormones. Many studies reported in the literature have used immunoassays, which cannot accurately or reliably distinguish between very similar compounds [23], and the reader of such studies therefore cannot be confident that the metabolite reported to have been measured was the only metabolite measured. This impediment has been overcome recently using gas chromatography-mass spectrometry (GC/MS) after high-pressure

liquid chromatography [8]. This method is sensitive and specific but requires specific skill and a significant amount of labor. There are few investigators that can measure these steroids at the very low levels present in humans, and the expense of measuring them is prohibitive for many investigators.

Additional challenges include the large number of factors that affect such levels. Primary among them is menstrual function variability in women of reproductive age. In such women, precursor hormones such as progesterone vary during the menstrual cycle, which may result in changes in the concentrations of its metabolites. Whether the ratio of the precursor hormones to its metabolites changes during the menstrual cycle or is altered in affective disorders is not known. Nor is it known whether such alterations might have clinical significance. In addition, we do not know whether blood or even CSF levels of neurosteroids reflect brain levels and whether or how such levels may vary between brain regions.

Finally, it should be noted that challenges also exist to the development of neuroactive metabolites for therapeutic use. Allopregnanolone has a very short half-life and is degraded by stomach acids. Therefore, in its unaltered form, it must be administered intravenously by continuous infusion. Natural precursors, such as pregnenolone, are being studied and can be purchased without a prescription as supplements or from compounding pharmacies; but pregnenolone is converted into progesterone and possibly other metabolites in addition to allopregnanolone; these may exert unwanted medical and psychiatric effects. Pregnenolone is therefore not as targeted a therapy, yet it may prove to be effective for some psychiatric disorders. Pharmaceutical companies have developed some – and are working on additional – oral formulations with adequate bioavailability that are not back-converted to precursor hormones, but these are not available by prescription or FDA-approved.

Clinical Application and Recommendation for Practitioners

Because the role of neuroactive steroids in the development and treatment of depressive disorders has not been established, and the FDA has not approved any neuroactive steroid medications for use, the prescription of such medications in clinical practice cannot be recommended at this time. However, given the promising nature of the research findings outlined above, practitioners may wish to consider referring patients who have been refractory to standard antidepressant therapies to clinical trials, when appropriate and available.

FAQs: Common Questions and Answers

Q1. What is a "neuroactive steroid"?

A1. A neuroactive steroid is a metabolite of a gonadal steroid, such as progesterone, that acts through traditional neurotransmitter receptor pathways. The most commonly studied neuroactive steroid is allopregnanolone, a metabolite of progesterone that acts at $GABA_A$ receptors with approximately 20 times the potency of benzodiazepines.

Q2. Is a relative neuroactive steroid deficiency a cause of depression?

A2. This is unknown. Small studies have suggested that mean CSF and blood levels of allopregnanolone are relatively lower in patients with depression than in non-depressed controls. Therefore, a relative deficiency of such endogenous neuroactive steroid levels is a possible contributor to depression symptom severity. Additional research is needed to determine whether this is the case.

Q3. Why would depressed patients develop a relative deficiency of neuroactive steroids?

A3. The answer to this question is not known but may involve relative blockades of enzymes that convert their precursor hormones (steroid hormones, such as progesterone) into neuroactive steroids.

Q4. Are neuroactive steroids available for prescription or over-the-counter?

A4. Pharmaceutical companies are developing and studying preparations of unaltered neuroactive steroids and neuroactive steroid analogs. None of these are FDA-approved or commercially available. Some neuroactive steroid preparations, such as pregnenolone, are available over-the-counter as supplements or through compounding pharmacies. However, none have been well studied, and side effects – especially with long-term use – are unknown. In addition, appropriate (safe and effective) doses have not been determined. In addition, over-the-counter and compounded products may have variable hormone content between batches and relative to what is stated on the label. Therefore, the use of these products cannot be recommended at this point in time.

Q5. Are neuroactive steroids "natural"?

A5. Yes. Neuroactive steroids are endogenous, meaning that they are made by the human body. Therefore, the concept that a relative deficiency may contribute to some affective disorders, and that replacement of these hormones may be developed therapeutically, has appeal. Some of the neuroactive steroid medications being developed have been altered chemically from the endogenous compound, for example, to prevent conversion back to precursor compounds, to increase their half-lives, or to make them bioavailable orally.

Q6. What are the next steps in understanding whether neuroactive steroids could be therapeutic options?

A6. Further research is needed and ongoing. Additional research funding and interest from patients in participating in clinical trials will advance the field more quickly. Such studies should elucidate normal physiology, delineate normal levels of these hormones, seek to understand whether blood levels accurately reflect brain levels, investigate specific brain targets, and elucidate mechanisms of action.

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