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Special Topics in Neuroendocrinology Allopregnanolone: Pathophysiology, Effects on Mood, Emerging Treatments

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Special Topics in Neuroendocrinology

Allopregnanolone: Pathophysiology, Effects on Mood, Emerging Treatments

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KEY POINTS

- Allopregnanolone is a neurosteroid and metabolite of progesterone that has been shown to play a role in mood regulation.
- Low levels and rapid declines in this neurosteroid are associated with mood disorders such as those within the menstrual cycle, postpartum depression, chronic stress, anxiety, post-traumatic stress disorder, and major depression. Studies have also linked it to mood-related aspects of addiction.
- Medications that increase allopregnanolone, such as serotonin reuptake inhibitors and Brexanolone, are correlated with improved symptoms. These medications represent established and newly developed drugs that increase its level and are currently used for treatments of mood disorders.
- Additional research into the relationship between allopregnanolone and mood regulation can provide promising new avenues for therapy.

INTRODUCTION

Allopregnanolone is a neuroactive steroid that has been associated with mood regulation and pursued as the focus of treatments in recent years. Low levels of this neurosteroid are observed in individuals with menstrual cycle disorders, postpartum depression, chronic stress, anxiety, post-traumatic stress disorder, and major depression.[1,2,5,9] In addition to low levels, a significant and acute decline in concentration has been connected to mood disorders associated with the menstrual cycle and during the postpartum period.[4, 5] Likewise, studies have begun to apply these findings to mood regulation within addiction.[3] This metabolite of endogenous progesterone exerts its potentiating effects notably on the gamma-aminobutyric acid (GABA)

neurotransmitter, specifically on the GABA-A receptor.[1] Through this connection, it is an important modulator of the GABA pathway and thus contributes to inhibitory effects on the central nervous system (CNS). It has also been identified in hypothalamic-pituitary-adrenal axis regulation and homeostasis.[2] These pathways that are influenced by allopregnanolone play important roles in mood regulation. Research has further shown that treatments acting on these pathways for these disorders result in increased allopregnanolone production.[6, 13] In observing the relationship between progesterone's metabolite and mood disorders, it is important to consider current pharmacologic interventions that modulate this pathway such as progesterone-based contraceptives. The foundational pathophysiology of allopregnanolone and its correlation with mood regulation has been identified and treatments involving modulation of this neurosteroid are recently being explored.[1,11,13] The purpose of this article is to provide an introduction and summary of current knowledge on this newly investigated hormone.

FLUCTUATIONS OF ALLOPREGNANOLONE

Allopregnanolone is synthesized through a series of enzymatic interactions converting cholesterol into progesterone and ultimately into allopregnanolone.[1] Generally, its levels exhibit a positive correlation with progesterone - increasing as progesterone increases and decreasing as progesterone decreases.[1] However, it's important to note that the production of allopregnanolone from progesterone is coupled alongside the production of other progesterone metabolites and influenced by levels of enzymatic activity.[1] One of the more well-studied enzymes which plays a role in this conversion is 5α-reductase.[7] With high enzymatic activity, more progesterone is converted into products like allopregnanolone.[1,7] When 5α-reductase activity is low, less

allopregnanolone is produced from progesterone.[1,7] These levels fluctuate on a continuum and are influenced by many factors both endogenously and exogenously.

Acute and chronic stress states alter levels of this neurosteroid and its effects on the GABA-A receptor.[7] In women, it fluctuates with the menstrual cycle and during the peripartum stages.[4,5] This relationship is beginning to be explored with regard to premenstrual dysphoric disorder and postpartum depression.[4,5] These findings show the cyclic nature of allopregnanolone along with progesterone in women and identify mechanisms affecting these levels through both the GABA pathway and hypothalamic-pituitary-adrenal axis.

CHANGES WITHIN THE MENSTRUAL CYCLE

The fluctuation of allopregnanolone is predictable due to its close association with endogenous progesterone. As previously described, its levels often are elevated or decreased with those of progesterone.[1] When considering the menstrual cycle, increased levels of the neurosteroid are present during the follicular phase and peak during the luteal phase.[4] After the luteal phase, there is a rapid decline in concentration along with a decline in progesterone.[8,12] A study by Kimball et al.[4] shows that while both hormones increase and decrease together, the ratio between allopregnanolone and progesterone decreases eightfold rather than in proportion. It is observed that less progesterone is converted into allopregnanolone. The precise mechanism behind the disproportional fluctuation and its effects are not yet clearly defined. It is hypothesized, however, to be in part due to the saturation of the enzyme 5α-reductase, limiting the metabolism of progesterone.[7]

As previously mentioned, the rapid decline in allopregnanolone has been suggested to play a role in menstrual disorders such as premenstrual syndrome and premenstrual dysphoric

disorder.[4] Mood dysregulation as it relates to the menstrual cycle, is most consistently associated with the luteal phase when hormones are declining.[4] Although this drop has been linked to mood dysregulation among certain individuals, Gilfarb et al.[8] highlight the importance of fluctuations in hormones such as allopregnanolone on brain plasticity. The natural change throughout the menstrual cycle reflects this biological need for hormone variation. The significance between allopregnanolone and individuals with premenstrual mood disorders requires further investigation into the rate of decline of this neurosteroid in the luteal phase, their concentrations and ratio to progesterone, and metabolism by 5α-reductase.

PERIPARTUM STATES

The rapid decline in allopregnanolone concentrations postpartum has been implicated with postpartum depression (PPD) and has recently been explored as the focus of pharmacological treatments.[5] Elevated progesterone and allopregnanolone levels are maintained throughout pregnancy, and in postpartum, these levels dramatically decline.[5] In studies on the relationship between hormone concentrations and PPD, research has not been able to show a direct connection between low allopregnanolone and PPD consistently.[9] Rather, they suggest the dramatic decline in its levels during postpartum period plays a larger role rather than the concentrations themselves.[9] Despite these inconclusive findings, medication increasing the levels of allopregnanolone has shown clinically significant improvements in patients experiencing postpartum depression.[13] With this evidence, there is a clear correlation between rapid declines in allopregnanolone and the incidence of postpartum depression, and improvements are seen with the repletion of this neurosteroid.

STRESS, ANXIETY, AND MAJOR DEPRESSION

During acute stress states, a temporary increase in allopregnanolone is observed alongside the activation of the GABA pathway.[9] Acute stress periods are expected in everyday life events and allopregnanolone appears to influence the CNS inhibitory pathway as a compensatory mechanism. Alternatively, during chronic stress, studies suggest desensitization of the receptors to allopregnanolone.[7] This desensitization causes its concentrations to decrease.[7] Almeida et al.[2] summarizes the changes in hormone synthesis seen in chronic stress states such as major depression and post-traumatic stress disorder. In this review, decreased allopregnanolone levels are linked to mood dysregulation during chronic stress. This is hypothesized to be due to a reduction in the conversion of progesterone to its metabolite.[2] Low allopregnanolone levels are measured without a decrease in progesterone suggesting a decrease in the synthesis of the neurosteroid metabolite. This is further represented in a recent study by Dichtel et al.[10] which compares allopregnanolone levels with the severity of anxiety and depression in women of different body mass indices. This study found low allopregnanolone levels to be associated with increased severity of mood dysregulation, independently of progesterone levels.[10] Current research[1,2,4,5,6] identifies a relationship between low allopregnanolone and mood dysregulation, however, the mechanism behind this suppression requires further investigation.

CURRENT TREATMENTS MODULATING ALLOPREGNANOLONE

Several pharmacologic treatments have been shown to alter allopregnanolone levels. Notably, SSRIs have been the cornerstone for the treatment of mood disorders and it has been recently proposed to work in part by elevating its levels.[6] The study by Uzunova et al.[11] found

allopregnanolone levels in patients with major unipolar depression normalize from a 60% deficit after SSRI treatment. This improvement was additionally reflected in their depression scores using the Hamilton Rating Scale for Depression.[11] When SSRIs are used as a treatment for premenstrual dysphoric disorder (PMDD) they take effect within days and are hypothesized to escalate the metabolism of progesterone, increasing the concentration of allopregnanolone.[12] As aforementioned, the symptoms of PMDD correlate with the luteal phase and rapid decline in allopregnanolone.[4] This proposed SSRI-driven increase in the neurosteroid is thought to stabilize patients during this vulnerable period.

Brexanolone is the only medication to work through allopregnanolone elevation primarily. This medication consists of a formulation given intravenously and is the first FDA-approved treatment specific for postpartum depression.[13] While the safety and long-term efficacy of this medication are still under investigation, this medication emphasizes allopregnanolone's direct effects on mood stabilization.[13]

ADDITIONAL CONSIDERATIONS

Addiction medicine is another area in which the influence of this neurosteroid is being explored. A double-blind randomized study by Milijov et al.[3] examined the effects of progesterone administration on allopregnanolone levels, cortisol stress response, and cocaine cravings in treatment-seeking individuals. As predicted, the administration of progesterone increased allopregnanolone levels.[3] This increase was shown to be equivalent in both males and females.[3] Furthermore, the participants demonstrated clinically significant improvements in stress responses and reductions in cravings.[3] This study reveals the parallels in pathophysiology

and effects of allopregnanolone across sexes. It also reveals promising areas for future research on allopregnanolone and mood dysregulation within the area of addiction medicine.

There are several points of note when considering pharmacotherapy modulating hormone levels. While studies on progesterone and allopregnanolone most consistently exclude participants using hormonal contraceptives, the effects of synthetic progestins on endogenous progesterone have been well-studied. Hormonal contraceptives lower endogenous progesterone levels through influence on the hypothalamic-pituitary-adrenal axis and negative feedback mechanisms.[14] Preliminary studies have seen a predictable decline in allopregnanolone with this decrease in endogenous progesterone.[8] Current research on this neurosteroid and its connection to mood regulation brings to light the need for studies on contraception-related suppression of allopregnanolone and its effect on mood disorders.

CONCLUSION

Distinct associations have been made between allopregnanolone and mood regulation. It has been implicated in a diverse scope of disorders when at low or acutely declining levels, and improvements are evident when concentrations increase. Several mechanisms regulate the synthesis of allopregnanolone including progesterone levels, enzymatic activity, and feedback mechanisms in the HPA-axis and GABA pathway. This emphasizes the need for more comprehensive research on the outside influences that lead to these changes. Low levels of this neurosteroid, its ratio to progesterone, and the rate of concentration decline are all linked to various mood disorders. With further research, the mechanisms behind allopregnanolone's relationship to mood dysregulation can be identified. Current treatments that increase

concentrations of allopregnanolone have been identified and there is great therapeutic potential with an increased understanding of this neurosteroid.

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