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Progesterone, Neurosteroids, and the Hormonal Basis of Catamenial Epilepsy

Women with epilepsy often report an increase in seizures at the time of menstruation. Such catamenial seizure exacerbations were noted in the Hippocratic Corpus, the classical texts of Greek medicine.¹ Sir William R. Gowers in his 1881 treatise on epilepsy wrote that whereas the relationship of seizures to menstruation “is a subject on which various opinions have been ex-

pressed” in more than half of the cases investigated “the attacks were worse at the monthly periods.”² Modern researchers generally have found that approximately 70% of women with epilepsy experience menstrual cycle–related fluctuations in seizure occurrence, and one third fit the strict criterion of doubling in frequency proposed by Herzog and colleagues³ as a definition of catamenial epilepsy. Catamenial seizure exacerbations are most common in the perimenstrual period, but they also can occur at the time of ovulation, and in the second half of “inadequate luteal phase cycles,” a condition (which may be more frequent in women with epilepsy⁴) in which the corpus luteum secretes subnormal amounts of progesterone but normal estrogen. Despite the high prevalence, clinicians often discount reports from their female patients of menstrual seizure worsening, probably because self-reporting is considered to be unreliable diagnostic criteria and treatment options are not widely recognized, and there is a belief that the condition does not have a firm scientific basis. In recent years, considerable progress has been made toward defining the hormonal factors that contribute to menstrual cycle–related fluctuations in seizure susceptibility, and specific treatment approaches are under rigorous evaluation. These developments should motivate clinicians to have a greater index of suspicion and a more compassionate attitude in treating women who are affected.

Although a variety of nonendocrine mechanisms such as fluctuations in antiepileptic drug levels and changes in water and electrolyte balance have been proposed as causes for catamenial epilepsy, the best established causative factors are hormonal, and there is particularly strong evidence implicating cyclic changes in serum progesterone. The relationship was first suggested in 1956 by John Laidlaw who analyzed the records of 50 unselected women inpatients in a suburban London epilepsy hospital whose seizure and menstrual records were available over a 25-year period encompassing more than 9,000 menstrual cycles.⁵ Laidlaw noted an “increased incidence [on average by as much as 45%] of fits immediately before, during, and after menstruation” and a reduction in the expected frequency by as much as 30% in the midluteal phase. Recognizing that progesterone levels are highest in the midluteal phase and decrease abruptly at menstruation, Laidlaw reasoned that catamenial epilepsy “could be explained if it were assumed that progesterone exerted a slight but significant anticonvulsant action.” Laidlaw’s hypothesis was supported by Torbjörn Bäckström’s findings of a negative correlation between plasma progesterone and seizure frequency, with the greatest increase in seizures corresponding to the rapid progesterone decline at menstruation.⁶ Note that Bäckström also observed a relationship between the preovulatory estrogen surge and an increase in seizures at mid-

cycle, leading him to conclude that estrogen activates seizures.

Not long after progesterone was chemically identified by the German chemist Adolf Friedrich Johann Butenandt and 14 years before Laidlaw’s prescient suggestion regarding the role of progesterone in catamenial epilepsy, Hans Selye in 1942 reported that progesterone had anticonvulsant properties in rats.⁷ In succeeding decades, as the molecular actions of progesterone were being characterized, the mechanism underlying this remarkable observation remained a mystery. Progesterone is secreted by the corpus luteum and serves various roles in female reproductive function, which are mediated mainly by binding to progesterone receptors target cells, such as those of the endometrial epithelium. When complexed with progesterone, progesterone receptors, members of the nuclear receptor superfamily of transcription factors, associate as dimers to specific DNA sequences (progestin response elements) in target genes, thereby altering the rate at which these genes are transcribed. However, the anticonvulsant effects described by Selye occurred within minutes, too rapidly to be caused by alterations in gene transcription. In the mid-1980s it was found that a progesterone metabolite allopregnanolone, often referred to as a “neurosteroid,” is a powerful positive allosteric modulator of GABA_A receptors⁸ (Fig). As with other agents that act to enhance GABAergic inhibition, allopregnanolone has anticonvulsant properties.⁹ Thus, it seemed possible that the anticonvulsant activity of progesterone could be because of its conversion to allopregnanolone. This conjecture was proved in animals using finasteride, a 5 α -reductase inhibitor, to block the first step in the conversion of progesterone to allopregnanolone¹⁰ and more recently confirmed in female mice with an induced null mutation in a 5 α -reductase gene.¹¹ Moreover, in an animal model of perimenstrual catamenial epilepsy, it was demonstrated that withdrawal of allopregnanolone (like that which occurs at menstruation in concert with decreasing levels of progesterone) is associated with a marked increase in seizure susceptibility.^{12,13} This is in part undoubtedly because of the loss of the anticonvulsant effects of allopregnanolone, but there also may be changes in the properties of GABA_A receptors that predispose to heightened seizure susceptibility.^{14,15} During this seizure-prone state, the activity of conventional antiepileptic drugs is reduced, possibly accounting for the clinical impression that catamenial seizures are unusually drug resistant.¹⁶ In contrast, neurosteroids that positively modulate GABA_A receptors actually have enhanced anticonvulsant potency in the model, providing support for a “neurosteroid replacement” approach to the treatment of perimenstrual catamenial epilepsy with either natural neurosteroids or synthetic analogs,¹⁷ or with progesterone to act as a precursor. The avail-

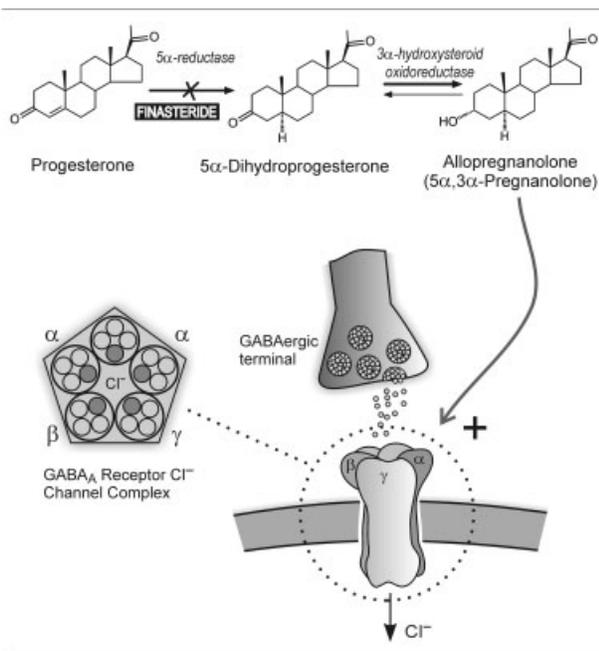


Fig. Biosynthetic pathway for the endogenous neurosteroid allopregnanolone. Finasteride, a 5 α -reductase inhibitor that is used clinically to inhibit conversion of testosterone to the more potent androgenic steroid dihydrotestosterone in the treatment of benign prostatic hyperplasia and male pattern hair loss, also blocks production of allopregnanolone from progesterone. Two isoenzymes contribute to 5 α -reductase activity in mammals.²¹ In humans, finasteride is a more potent inhibitor of the type II isoenzyme (predominantly expressed in the male urogenital tract) than the type I isoenzyme (liver, skin, and brain), but its specificity is not absolute.²² At doses of 1 to 5mg/day, finasteride inhibits approximately 70% of steroid 5 α -reducing activity in men and women.^{23,24} Allopregnanolone formed in peripheral tissues readily enters the brain where it acts to enhance activation of GABA_A receptors; there is evidence that allopregnanolone also can be formed locally in the brain. The pentameric structure of the GABA_A receptor is illustrated with a typical configuration of subunits each with four transmembrane domains including the pore-forming M2 domain (dark gray). GABA_A receptors are gated by GABA released from the presynaptic terminals of inhibitory neurons. Binding of allopregnanolone enhances the open probability of the intrinsic ion channel, enhancing Cl⁻ flux and promoting synaptic inhibition.

able clinical evidence suggests that the latter approach is promising,¹⁸ and a multicenter placebo-controlled trial is in progress. Although progesterone is relatively well tolerated, hormonal side effects such as breast tenderness can occur and a short serum half-life makes it inconvenient to administer; neurosteroid analogs that do not mimic progesterone's genomic actions and have improved pharmacokinetic properties may overcome these drawbacks.

A brief report in this issue of the *Annals* by Herzog and colleagues¹⁹ provides anecdotal evidence support-

ing the concept that progesterone's therapeutic activity in catamenial epilepsy requires conversion to a 5 α -reduced metabolite. A woman with catamenial epilepsy and polycystic ovary syndrome was being treated with progesterone, which improved her seizure control. Unbeknownst to her epileptologist, another physician began giving her finasteride, and a drastic increase in seizure frequency and severity ensued. Ordinarily, finasteride is contraindicated in women of reproductive age because it inhibits the conversion of testosterone to the more potent androgen dihydrotestosterone and may impair virilization of a male fetus, but it often is used in the hyperandrogenic state of polycystic ovary syndrome. The unintentional experiment represented by this case report is the first direct evidence that endogenous neurosteroids can regulate seizure susceptibility in humans and should serve as an impetus for further exploration of neurosteroid-based epilepsy therapies, for which there is already preliminary evidence of efficacy in non-menstrual-related seizure disorders.²⁰

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