Neurosteroids on the Epilepsy Chessboard — Keeping Seizures in Check

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**Endogenous Neurosteroid Synthesis Modulates Seizure Frequency.** Lawrence C, Martin BS, Sun C, Williamson J, Kapur J. *Ann Neurol* 2010;67(5):689–693. Inhibitory neurosteroids, molecules generated in glia from circulating steroid hormones and de novo from cholesterol, keep seizures in check in epileptic animals. They can enhance inhibitory transmission mediated by γ-aminobutyric acid receptors and have anticonvulsant action.

**COMMENTARY**

The steroid hormone progesterone has long been known to have anticonvulsant properties. Seizure protection is not conferred by progesterone itself, but rather by the progesterone metabolite allopregnanolone, a member of a class of endogenous steroids commonly referred to as neurosteroids (1). Neurosteroids do not have traditional hormonal activity. Rather, allopregnanolone and other similar neurosteroids act as positive allosteric modulators and direct activators of GABA<sub>A</sub> receptors. Like other such GABA<sub>A</sub>-receptor modulators,
allopregnanolone is a powerful anticonvulsant. Although neurosteroids act on all GABA_\text{A}-receptor isoforms, including those localized at synapses, they produce especially large effects on nonsynaptic δ-subunit containing GABA_\text{A}-receptor isoforms. Recent evidence indicates that neurosteroids are present predominantly, if not exclusively, in principal (excitatory) neurons in many brain regions that are relevant to focal epilepsies, including the hippocampus and neocortex (2). All of the enzymes required for neurosteroid synthesis are expressed in the brain. Although it had previously been speculated that brain neurosteroidogenesis occurs in astrocytes, new immunohistochemical evidence indicates that GABA_\text{A}-receptor modulatory neurosteroids may not be present in glia or in nonpyramidal neurons (i.e., interneurons). The highly restricted distribution of neurosteroids to excitative neurons suggests that they are mainly derived from local synthesis and not from the circulation, although it is clear that peripheral neurosteroids do easily cross the blood–brain barrier.

The factors that regulate local neurosteroid synthesis are obscure. However, since GABA_\text{A} receptors are also localized to principal neurons, neurosteroids may serve an autocrine role to influence the functional activity of the very neurons in which they are synthesized. Recently, evidence has accumulated that neurosteroids influence GABA_\text{A} receptors by binding to discrete sites on the receptor complex located within the transmembrane domains of α and β GABA_\text{A}-receptor subunits (3) and that they access these sites by lateral membrane diffusion (4). Neurosteroids are viewed as high-potency modulators of GABA_\text{A} receptors, since they are effective at concentrations in the range of 1 μM and below in aqueous solution. However, neurosteroid binding to the GABA_\text{A} receptor is of low affinity (K_d, ~1 mM), and the high effective potency of neurosteroids results from partitioning of the lipophilic steroids within the plasma membrane, such that the concentrations presented to the receptor are orders of magnitude greater.

Given the emerging understanding of the role of neurosteroids as autocrine modulators of neuronal excitability, the question arises as to whether endogenous neurosteroids regulate seizure susceptibility. Lawrence et al. provide important new evidence that the availability of neurosteroids does indeed critically influence the propensity for seizures. These investigators used epileptic female rats that had experienced a prolonged bout of status epilepticus induced by lithium-pilocarpine treatment. Spontaneous seizure activity was monitored by continuous video-EEG recording. The epileptic animals exhibited about six seizures per day, each lasting approximately a minute. However, when neurosteroids were withdrawn, using the neurosteroid synthesis inhibitor finasteride, an enormous (more than ten-fold) increase in seizure frequency was observed. In contrast, finasteride—a selective inhibitor of 5α-reductase, the first and rate-limiting enzymatic step in the synthesis of neurosteroids from their steroid hormone precursors (e.g., progesterone)—did not induce seizures in normal animals.

Similarly, there is no evidence that finasteride causes seizures in humans who do not have epilepsy. Finasteride is used clinically for the treatment of benign prostatic hypertrophy and male pattern hair loss. Seizures have not been reported as an adverse event of finasteride treatment, and given the long experience with the drug, it is safe to say that it does not cause epilepsy. It is also noteworthy that individuals with congenital 5α-reductase deficiency, caused by a mutation in the 5α-reductase type 2 gene (a condition with ambiguous genitalia), do not exhibit epilepsy. Although neurosteroid deficiency does not induce epilepsy, there is evidence that neurosteroids can modulate epileptogenesis (5).

While finasteride does not provoke seizures in the general population, there are no prospective studies to determine whether inhibition of 5α-reductase by finasteride influences seizure susceptibility in individuals with epilepsy. There is a single anecdotal report of a woman with epilepsy taking finasteride for male pattern baldness who experienced an increase in seizure frequency and severity in association with finasteride use (6). The doses of finasteride used clinically are in the range of 1 to 5 mg per day, which is far less than the doses of 30 to 100 mg/kg used in rats in the study by Lawrence et al. Furthermore, in humans, finasteride is selective for the type 2 5α-reductase isoform and less active on the type 1 enzyme that is the isoform predominantly present in the brain. This selectivity is not observed with the rat enzymes. In sum, finasteride, as administered clinically in humans, probably does not block neurosteroidogenesis sufficiently to influence seizure susceptibility under most circumstances.

When neurosteroid levels fluctuate, loss of seizure control can occur. A key clinical situation in which neurosteroids are a factor in seizure control is perimenstrual catamenial epilepsy. Rodents have a 4 to 5 day estrous cycle and studies of fluctuations in seizure susceptibility in cycling female rodents have not led to results that are relevant to the human menstrual cycle. In order to study the neurobiological basis of catamenial epilepsy and develop treatment approaches, a rat model was developed both to simulate the prolonged exposure to high levels of estrogen and progesterone that occur in the luteal phase of the 28-day human menstrual cycle as well as to replicate the withdrawal of allopregnanolone that occurs in conjunction with the fall in progesterone levels at the time of menstruation (7). Prolonged elevated sex hormone levels are induced by gonadotrophin treatment, and 11 days later allopregnanolone is withdrawn by treatment with finasteride. Lawrence et al. utilized the catamenial epilepsy model in epileptic rats. They found an even greater exacerbation of seizures than ordinarily occurs.
in epileptic animals. This finding suggests that prolonged exposure to neurosteroids (and perhaps other hormonal changes in the catamenial epilepsy model) leads to heightened excitability in the epileptic brain that is revealed when the neurosteroids are withdrawn. A key alteration that has been associated with chronic neurosteroid exposure and could be a contributing factor is down-regulation of δ-subunit containing nonsynaptic GABA\(\text{A}\) receptors (8).

Lawrence et al. conducted a final experiment in ovariec-tomized epileptic animals that had low serum progesterone levels maintained by subcutaneous implantation of a proges-terone pellet. Unexpectedly, these animals also exhibited a huge (25-fold) increase in seizure frequency following finasteride treatment. Unfortunately, the authors did not study animals in which peripheral progesterone was completely eliminated. Nevertheless, the results of this last experiment suggest that the exacerbation of seizures that occurs following finasteride treat-ment is due to the inhibition of brain neurosteroid synthesis and is not caused by suppression of the conversion of peripheral (ovarian) progesterone to allopregnanolone. This important conclusion focuses attention squarely on brain neurosteroids as critical regulators of seizures in epilepsy. Clearly, more needs to be learned about the role of locally synthesized neurosteroids in epileptic brain circuits.

The paper by Lawrence et al. also has important impli-cations for therapy. The authors demonstrate that allopreg-nanolone treatment rapidly terminates the finasteride-induced exacerbation of seizures, providing additional evidence that the increase in seizure frequency is because of a finasteride-induced reduction in neurosteroids and not some other action of the drug. More importantly, it supports the concept that neurosteroid replacement may be useful in the treatment of seizures associated with neurosteroid fluctuations, such as catamenial epilepsy (7). In catamenial epilepsy, breakthrough seizures occur despite treatment with antiepileptic drugs. Previous studies (reviewed in 7) and the new results from Lawrence et al. support the potential of neurosteroids as a novel treatment approach for these pharmacoresistant seizures.

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References