

## **Seizing an Opportunity: Broader Definitions of Epilepsy May Lead to Better Treatments**

**By Helen E. Scharfman, Ph.D.**

*Editor's note: There is not just one type of epilepsy. While some forms of the disease are characterized by convulsive seizures, others involve seizures that are barely noticeable. Seizures can occur for many reasons: they can be caused by genetic mutations, injury, or infection early in life. In addition, events in daily life, such as stress, or normal variations in hormones, such as estrogen and testosterone, can influence brain activity and therefore influence seizures. By considering the powerful interactions between the brain and the endocrine system, this influence of hormones on seizures can be understood and new treatment options can be considered.*

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A common misconception is that a seizure involves sudden, uncontrolled movements or convulsions. However, convulsions do not always accompany seizures. One type of epilepsy—absence epilepsy—is characterized by seizures that involve little movement at all, only a blank, expressionless gaze. For a brief period, the person experiencing the seizure is unresponsive, or “absent.” These seizures are not easy to recognize and may therefore go undetected. Even the person having the seizure may not notice it, because consciousness is temporarily interrupted during an absence seizure.

The diversity in the types of seizures has led to difficulty in classifying them. It is often hard to bring seizures under control because there are many causes, some of which are not well understood. Fortunately, in the past few decades clinical and laboratory research has led to a better understanding of the diversity of seizures and the causes of epilepsy. This diversity has led some researchers to suggest that epilepsy might more accurately be considered a spectrum disorder.<sup>1</sup> The concept of a spectrum has been used to describe other disorders, such as autism, that are characterized by a wide range of symptoms. In epilepsy and autism, the fundamental symptoms (seizures in epilepsy, certain behaviors in autism) can range extensively in type, severity, and cause.

The idea that epilepsy is a spectrum that includes many types of seizures, sometimes without any obvious signs, also helps explain why the disease is so hard to treat. For example, in women with catamenial epilepsy (epilepsy in which seizures worsen at specific times of the menstrual cycle), anticonvulsant drugs may control seizures almost all the time, except during these specific times of their menstrual cycle.<sup>2</sup> During pregnancy, when the hormones estrogen and progesterone increase dramatically, women often report a change in seizures.<sup>3,4</sup> Changes in seizure frequency or severity also occur when people with epilepsy enter menopause (in women) and andropause (in men), a phenomenon that has been explained by falling levels of the reproductive hormones estrogen, progesterone, and testosterone.<sup>3-6</sup>

This effect of hormones on seizures has been known for more than a century. In light of the increasing understanding of the intimate relationship between the brain and the endocrine system, we can now explain it better. Below, some of the current ideas about how the brain is affected by reproductive hormones are discussed, using estrogen and progesterone as examples. Then the menstrual cycle is addressed, and the way in which scientists have used the understanding of estrogen and progesterone to explain why seizures increase at certain times of the menstrual cycle. Finally, the concept that epilepsy is a spectrum is used to shed light on some

of the persistent questions about catamenial epilepsy, and to suggest potential treatments that have not yet been considered to help women who have the condition.

### **The Brain and Reproductive Hormones**

The relationship between the gonads (ovaries and testes) and the brain is complicated. It is not surprising that we still do not completely understand all of the effects of hormones on the brain or on seizures. However, a great deal has been clarified in the last decades of research.

Reproductive hormones like estrogen, progesterone, and testosterone have profound effects on the brains of both men and women, even in parts of the brain that are not considered to be critical to reproduction. Moreover, these effects occur throughout life, not only in adulthood. During early stages of development, reproductive hormones like estrogen and testosterone are critical. Researchers have shown that in laboratory animals, estrogen levels in the fetus are critical to the gender of the fetus.<sup>7</sup> After puberty, levels of circulating estrogen and testosterone also affect the brain; the interplay between the early, “organizational” effects and the postpubertal, “activating” effects of hormones mediates the net effect of hormones in the adult brain.<sup>8,9</sup>

Besides being synthesized in the gonads, estrogen, progesterone, and testosterone can be synthesized elsewhere, including in the brain itself. Such synthesis can potentially occur anywhere in the brain because it occurs in astrocytes, cells that are located in all areas of the brain. Astrocytes have historically been considered supportive cells, responsible for housekeeping in the brain (cleaning up debris, removing damaged cells or infection). We now know that astrocytes have many other functions, including the synthesis of hormones, because enzymes in astrocytes metabolize cholesterol, a component of the outer membranes of all cells, into hormones.

But we do not yet understand exactly how each hormone influences the brain. We do know that both estrogen and testosterone have many effects on the brain, influencing neurotransmitters (which allow neurons to communicate) and neuronal activity.<sup>10,11</sup> Hormones also have metabolites that have effects on brain activity. For example, allopregnanolone, a metabolite of progesterone, inhibits neuronal activity in many areas of the brain. As a result, it has been suggested that progesterone would be help stop seizures.<sup>12</sup>

Because reproductive hormones affect brain activity, the changes in hormones at puberty, pregnancy, or during the menstrual cycle are important to consider when treating women with

epilepsy. Treatment is complicated, however, because hormones like estrogen and progesterone do not affect all patients in the same way. For example, some women experience changes in the severity and frequency of seizures in relation to estrogen or progesterone treatment, but others do not. Similarly, some women have seizures that worsen during part of their menstrual cycle, but some do not. The reasons for these variations are unclear. Furthermore, some effects of hormones on seizures that have been demonstrated in laboratory experiments are not reproducible. For example, sometimes estrogen appears to promote seizures, but it doesn't always.<sup>12</sup> Besides confusion, this has led to frustration, because clinicians are unsure how to treat patients whose seizures have suddenly worsened, possibly because of changes in reproductive hormone levels. Nevertheless, our understanding of effects of estrogen and progesterone on the brain has led to hypotheses that explain why seizures can increase at certain times during the menstrual cycle.

### **Catamenial Epilepsy**

As mentioned above, catamenial epilepsy refers to seizures that worsen at particular times during the menstrual cycle. This syndrome has been recognized for more than 100 years, but it has been difficult to study.<sup>13</sup> Some investigators have even questioned whether catamenial epilepsy exists.<sup>14</sup> Many clinicians do not find robust sex differences in their patients,<sup>15-17</sup> and they therefore conclude that syndromes like catamenial epilepsy are not likely to be significant.<sup>13</sup>

However, clinical research provides strong evidence that catamenial epilepsy is common. Dr. Andrew Herzog, a leader in this field, estimates that catamenial epilepsy occurs in one-third of women with epilepsy.<sup>2</sup> A recent epidemiological study in Korea estimated that catamenial epilepsy occurs in almost 50 percent of women with epilepsy.<sup>18</sup> The accuracy of these estimations is hard to judge, however, because seizures that are unnoticed will be missed, leading to an underestimation of the number of women with catamenial epilepsy. Nevertheless, when the condition has been documented, symptoms are often the worst during the days just before the start of menstruation, approximately day 28 of the menstrual cycle, and the days just after the onset of menstruation—the perimenstrual period. Symptoms also worsen during the periovulatory phase, approximately day 14, when ovulation occurs (see Diagram 1, page 9).

The rise in circulating estrogen (serum estrogen) during the menstrual cycle affects the brain in many ways, and includes effects on neurons and non-neuronal cells such as astrocytes. In neurons, cell structure is affected—for example, dendritic spines are modified. Spines are

important because the spines receive excitatory input from other neurons and help neurons communicate with one another. Many scientists believe that a major effect of estrogen in the brain is increased neuronal activity because estrogen increases dendritic spines.

Circulating progesterone has many effects, because progesterone itself has actions on neurons, and its metabolite allopregnanolone does also. Allopregnanolone binds to receptors that are responsible for effects of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. Therefore, when progesterone rises during the menstrual cycle, it is thought that neuronal activity will decrease in many parts of the brain.

Most of our current understanding of the action of estrogen and progesterone involves the effects of these hormones within the brain, but they also affect many parts of the body that in turn alter brain activity. This complicated interplay between the brain and the rest of the body is one of the reasons epilepsy is hard to treat—it may not be a static condition but one that is constantly changing.

Several hypotheses based on effects of estrogen and progesterone that have been identified in the last decades have been offered to explain catamenial epilepsy. One is that seizures increase when the ratio of estrogen to progesterone is high.<sup>5,19,20</sup> This hypothesis explains the worsening of seizures during the periovulatory period and the relative resistance to seizures during the luteal phase (days 14–28—see Diagram 1, page 9), but it does not explain why seizures worsens during the perimenstrual period, because both estrogen and progesterone are low at that time.

An alternative view developed after it was shown that falling progesterone levels exert excitatory effects.<sup>21</sup> Researchers hypothesized that progesterone withdrawal occurs at the end of the menstrual cycle, leading to excitatory effects. Literally, there is a decrease in seizure threshold,<sup>22</sup> which is the point at which the brain has been sufficiently activated so that a seizure begins. In patients with epilepsy, this threshold is thought to be lower than in other people, so that even mild activation of the brain can lead to a seizure.

Seizure threshold can be evaluated by activating the brains of laboratory animals experimentally. Researchers investigated the notion of progesterone withdrawal by treating laboratory rats or mice with progesterone and then suddenly stopping the treatment. The results showed that a decrease in seizure threshold accompanied withdrawal of the treatment.<sup>21,22</sup> These data suggest that in a patient with epilepsy, seizures may be more likely after progesterone withdrawal because seizure threshold is lower. Subsequent studies, using other methods to

simulate progesterone withdrawal, and other means of evaluating seizure susceptibility, confirmed these findings.<sup>23,24</sup> Progesterone withdrawal therefore provides a potential explanation for perimenstrual seizures.

Further research into the effects of progesterone withdrawal has suggested that it is not simply a sudden drop in progesterone or its metabolite allopregnanolone that causes the increased susceptibility to seizures. Rather, progesterone withdrawal leads to a specific change in GABA<sub>A</sub> receptors, the neurotransmitter receptors that bind allopregnanolone. The GABA<sub>A</sub> receptor is normally composed of several components, or subunits. When progesterone withdrawal occurs, increased levels of one of the subunits stops allopregnanolone from having an inhibitory effect on seizure activity,<sup>25,26</sup> and other subunit changes lead to the resistance of seizures to some antiepileptic drugs, such as the benzodiazepines.<sup>27</sup>

Progesterone also affects other hormones, called mineralocorticoids. Mineralocorticoids normally allow the body to retain sodium, potassium, and, as a result, water. This is significant because water balance affects seizures: when neurons in the brain swell, they become closer together, increasing neuronal activity.<sup>28</sup> As a result, seizure threshold can decrease. During the menstrual cycle, water retention occurs during the end of the luteal phase. During this period, which coincides with the perimenstrual phase, seizure threshold may decrease because water retention increases neuronal excitability. This reasoning has led to the use of diuretics such as acetazolamide in women with catamenial epilepsy, although they have not been completely successful,<sup>29</sup> probably because they do not treat the other effects of hormones during the menstrual cycle.

Recent studies in female laboratory animals suggest that estrogen levels may also contribute to perimenstrual seizures, because estrogen can have effects on the perimenstrual period even if estrogen is elevated only in the preceding phases of the cycle. These delayed effects of estrogen could be mediated by genes that regulate neuronal activity. For example, estrogen increases the concentration of brain-derived neurotrophic factor (BDNF), a molecule that increases excitation in the brain. The increase in BDNF is long-lasting—it persists after estrogen levels have returned to normal.<sup>30</sup> Estrogen can therefore exert long-lasting effects on neuronal activity even if estrogen levels increase only briefly. High levels of BDNF throughout the luteal phase would result; this prediction is supported by clinical studies showing that BDNF is high during the luteal phase.<sup>31</sup> During the luteal phase, the actions of BDNF may be inhibited by progesterone and allopregnanolone, but at the end of the menstrual cycle, elevated BDNF

may persist after progesterone and allopregnanolone fall. The imbalance between excitatory effects of BDNF and inhibitory effects of progesterone and allopregnanolone would explain increased seizures during the perimenstrual period. It is also interesting that BDNF induces the synthesis of neuropeptide Y (NPY), which is considered to be a potential anticonvulsant.<sup>32</sup> The rise in NPY could truncate the effects of BDNF, ending the perimenstrual period. (For more about BDNF, see Diagram 2, page 9.)

These points are not only relevant to epilepsy. There are many neurological and psychiatric conditions in which symptoms worsen in relation to the menstrual cycle. Some scientists have suggested that the symptoms are caused by abnormal periods of activity in parts of the central nervous system (CNS), and resemble seizures. With regard to migraine headaches, for example, women often report that the most severe episodes follow a perimenstrual pattern. And during a migraine, abnormal patterns of brain activity develop. Another example is related to pain. Women who have chronic pain can experience the most severe pain during certain phases of the menstrual cycle. Pain may result from a period of hyperactivity in the areas of the CNS where pain is controlled. The concept of an epilepsy spectrum suggests that these types of hyperactivity of neurons in the CNS might be a part of the spectrum, even though pain has not been considered to be a type of epilepsy. Supporting this view is the observation that antiepileptic drugs are often successful in the treatment of migraine and pain.

### **Difficulties in Identifying Catamenial Epilepsy**

Why do only some women have catamenial epilepsy, and why, even among those women, is it sometimes difficult to document?

The type of epilepsy that is most susceptible to a catamenial pattern appears to involve a part of the brain (the temporal lobe) that does not control movement, so the seizures may not be convulsive.<sup>33</sup> There are a variety of nonconvulsive seizures, and they have different causes. Different areas of the brain are involved. In temporal lobe epilepsy, for example, seizures are often partial or complex partial: they can arise from one part of the temporal lobe and spread to other areas (but do not always do so), and they are not always accompanied by convulsions. These seizures often start with an aura—a sensation of déjà vu, for example, or an awareness of a familiar smell—and are usually accompanied by a temporary loss of consciousness. After the seizure, the person may be somewhat confused but subsequently resumes normal behavior.

Because a patient with temporal lobe epilepsy can have seizures without convulsions, the person can be unaware that a seizure occurred—he or she would have no memory of it. The person may also not remember the seizure because of the disruption of activity in the temporal lobe at the time of the seizure—the temporal lobe is important to normal learning and memory. It is easy to see that the prevalence of catamenial epilepsy could well be underestimated if the type of seizure activity that increases at particular times during the menstrual cycle is nonconvulsive.

The occurrence of catamenial epilepsy may also be underestimated because patients may experience nonconvulsive seizures in a catamenial pattern but their physicians do not know they occurred. In addition, physicians cannot be sure that all seizures patients report actually occur, because some people appear to imagine seizures—these are called pseudoseizures.<sup>34</sup> Most physicians would use an electroencephalogram (EEG) to document seizures, but some seizures may be missed by EEG if they involve structures deep in the brain, relatively far from the EEG electrodes, which are placed on the scalp, near the brain's surface. Some seizures may be missed if the abnormal brain activity is brief. And women may not be diagnosed with catamenial epilepsy if their menstrual cycle is not regular. Because chronic seizures can lead to irregular cycles, a woman and her physician may be unable to recognize a pattern.

### **Implications for Epilepsy Research**

The notion of a spectrum of epilepsy is not only important to women with epilepsy but relevant to research scientists who use laboratory animals to study temporal lobe epilepsy. In these animals, seizures that simulate those in patients with temporal lobe epilepsy are usually defined by five stages of convulsive seizures that were originally described in 1972.<sup>35</sup> The stages are easy to see because there are convulsions. It is hard for researchers to agree when an animal has a nonconvulsive seizure, in part because of the difficulty in defining the point at which normal brain activity has increased enough to constitute a seizure. By considering epilepsy as a spectrum ranging from mild to severe, and no longer requiring convulsions to define a seizure, research in epilepsy would broaden in scope, and ultimately many more people with seizures would be helped, such as those people who have seizures that are hard to detect.

This would be a very important paradigm shift. The more researchers can tell us about the spectrum of seizures in experimental animals, the better equipped we will be to treat the spectrum of seizure disorders that exist in people. In fact, some potential antiepileptic drugs may have been passed over in the last decades of drug screening because drugs are usually tested to

see if they stop convulsive seizures in animals. They are often not tested to see if they stop seizures without convulsions. And they are often not used to see if they help animals that are tested for other conditions where nonconvulsive seizures are suspected, such as Alzheimer's disease. Some candidate antiepileptic drugs might be successful against nonconvulsive conditions but would fail a drug screen because they are unable to ameliorate a convulsive seizure.

Restricting epilepsy research to the investigation of convulsive seizures is especially limiting for studies of hormones in female animals because convulsive seizures in female rodents stop the ovarian cycle or make it irregular. This effect has been documented for the common animal models of temporal lobe epilepsy.<sup>36-38</sup> As a result, it is hard to conduct research in female rodents to understand how epilepsy influences reproductive function. This is unfortunate, because women with epilepsy often develop reproductive problems, such as infertility or polycystic ovarian syndrome. Studying female rats with nonconvulsive seizures would provide more opportunities to understand the adverse effects of seizures on the reproductive system.

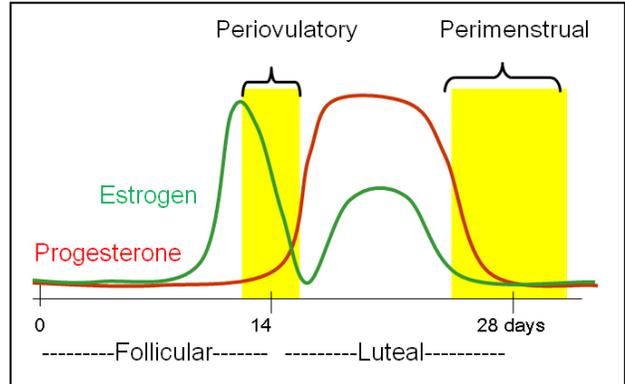
The idea of the epilepsy spectrum also has implications for the development of new drugs to treat epilepsy. It may be useful to develop drugs that block the consequences of estrogen and progesterone, rather than estrogen and progesterone themselves, because the hormones are very important to normal life. If a particular branch of BDNF signaling could be identified as the most important to seizure threshold, it might be a better endpoint to target. Another strategy would be to restore GABA<sub>A</sub> receptor subunits to their normal levels. This strategy could be used in concert with progesterone supplementation, or the enhancement of allopregnanolone levels. However, BDNF signaling and GABA<sub>A</sub> receptors are important to many normal functions. More specific targets than BDNF or the GABA<sub>A</sub> receptor are needed so that anticonvulsant actions occur without side effects. The more we can clarify the mechanisms underlying catamenial seizure exacerbation, the more likely it is that we can develop treatments without side effects.

## **Conclusion**

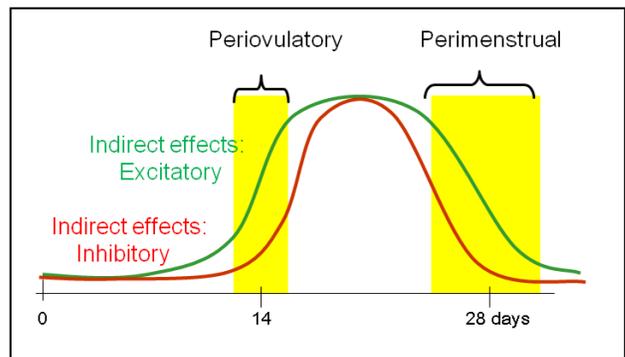
Epilepsy is a devastating illness that has far-reaching effects on patients and their families. Patients could be better helped by greater awareness of the epilepsy spectrum because nonconvulsive seizures would be better recognized. Deepening the understanding of the epilepsy spectrum could lead to more accurate diagnoses, possibly allowing the detection of epilepsy in individuals who would otherwise not be treated with anticonvulsants. Research would benefit by

the increasing recognition of the diverse types of seizures, which would lead to a broader focus on drugs that are not necessarily *anticonvulsant* but *antiepileptic*.

**Diagram 1.** The estrogen/progesterone hypothesis for catamenial epilepsy. A diagram of the time line of the menstrual cycle, which lasts 28 days, and is divided into a follicular phase and a luteal phase. The excitatory effects of estrogen and the inhibitory effects of progesterone have been used to explain the two times during the menstrual cycle when symptoms usually worsen: the periovulatory period, at approximately day 14, and the perimenstrual period, at approximately day 28 (yellow bars). Progesterone “withdrawal” has also been suggested as an explanation of perimenstrual seizures.



**Diagram 2.** Indirect effects of estrogen and progesterone that are excitatory (green) or inhibitory (red) provide an explanation for catamenial epilepsy. Indirect excitatory effects of estrogen include those mediated by brain-derived neurotrophic factor (BDNF). BDNF synthesis in the brain is induced by estrogen, and BDNF increases neuronal activity. Indirect inhibitory effects of progesterone (red) are mediated by its metabolite allopregnanolone, which increases the effects of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain. During the periods marked by the yellow bars, the excitatory effects (green) are greater than the inhibitory effects (red), which could lead to a decrease in seizure threshold.



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