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Temporal Lobe Epilepsy and the BDNF Receptor, TrkB

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Temporal lobe epilepsy (TLE) is a particularly devastating form of human epilepsy. The disorder is progressive in a substantial fraction of patients, which is demonstrated by increasing medical intractability, degeneration of cortical tissue, and cognitive impairment. Clinical observations by shrewd clinicians led to the proposal that seizures themselves constitute one factor that promotes worsening of the epileptic condition (1). Availability of animal models in which seizures themselves worsen the epileptic condition provides the opportunity to probe the underlying mechanisms. Insight into the cell surface receptors and downstream signaling pathways that promote epileptogenesis will hopefully provide valuable clues to the cellular mechanisms as well as novel targets for development of therapies aimed at limiting progression. Brain derived neurotrophic factor (BDNF) is a small (14 kD) secreted protein that binds to the ectodomain of its cognate receptor tyrosine kinase, TrkB. Binding of BDNF to TrkB induces receptor dimerization, activation of the receptor tyrosine kinase activity, the phosphorylation of select tyrosines in the cytoplasmic domain creating docking sites for adaptor proteins or enzymes that couple these receptors to intracellular signaling cascades. In diverse animal models of TLE, seizures induce striking increases of BDNF expression and enhanced activation of TrkB in the mossy fiber pathway of hippocampus. Intrahippocampal infusion of BDNF and transgenic overexpression of BDNF or TrkB increase seizure susceptibility or severity. Conditional knockout of TrkB eliminated epileptogenesis altogether in the kindling model. Interestingly, estrogen enhances BDNF expression within hippocampus and treatment of female rats with estrogen led to epileptiform responses of CA3 pyramidal cells to mossy fiber activation, an effect blocked by Trk antagonism. Collectively, these findings establish a causal role for BDNF and TrkB in limbic epileptogenesis and suggest that TrkB signaling may contribute to catamenial epilepsy.

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INTRODUCTION

One of the most difficult but most important goals in epilepsy research today is to address the underlying mechanisms that contribute to seizures. Another important issue is understanding epileptogenesis - the transformation of the normal brain to a chronic epileptic state. If these issues can be effectively addressed, the resultant insights may lead to the development of better AEDs to treat seizures, and antiepileptogenic drugs that can prevent the disease. Current AEDs target many ion channels known to contribute to neuronal excitability. This broad "net" can help reduce seizures, but also leads to side effects. Further, sometimes seizures cannot be controlled even with high doses of these drugs (pharmacoresistance). Mesial temporal lobe epilepsy (MTLE) is a good example of a condition with a complex set of causes, and a subset of patients who are pharmacoresistant. Therefore, understanding the mechanisms of MTLE has been a subject of avid interest. Combining a clear clinical characterization of MTLE with insights from research using animal models, as discussed below, has revealed a potential control point for new antiepileptic and antiepileptogenic therapy: the neurotrophic factor BDNF and its receptor, TrkB.

MESIAL TEMPORAL LOBE EPILEPSY: A PROGRESSIVE DISORDER IN HUMANS AND ANIMAL MODELS

MTLE, the most common form of partial epilepsy, is a progressive disorder in a substantial number of affected individuals (2,3). The progression is evident in part as persistence of disabling seizures despite anticonvulsant therapy, the refractoriness to therapy sometimes arising years after onset of the disorder (4). Progression is also evident as destruction of hippocampus and parahippocampal gyrus and temporal lobes as revealed in multiple MRI analyses conducted over time in patients with MTLE compared to normal controls (5). Additional evidence of progressive atrophy of neocortical gray matter has been demonstrated by an independent group of investigators using MRI analyses in a crossectional study of MTLE patients compared to age matched controls as well as a longitudinal study in which patients served as their own controls (6).

What underlies the progression of MTLE in this subset of affected individuals? An astute clinician, Sir William Gowers, proposed that seizures themselves contributed to the progression of epilepsy (1). Discovery of the kindling phenomenon, by Graham Goddard and colleagues (7), almost a century later, validated Gowers' idea. In this model, repeated induction of brief, focal seizures by chemical or electrical stimuli eventually results in longer and more severe focal and tonic-clonic seizures. Once established, this enhanced sensitivity to electrical stimulation persists for the life of the animal. While 15 or so stimulations (e.g., in the amygdala) are required to induce this lifelong enhanced sensitivity, additional stimulations (80+) lead to the emergence of spontaneous seizures (8,9) and destruction of cortical gray matter (8). That is, periodic induction of isolated seizures (e.g. at daily intervals) in an animal model is sufficient to induce progressive increase in severity of evoked seizures, emergence of spontaneous seizures, and destruction of cortical gray matter (10). Indeed a progressive increase of seizure frequency is evident in a diversity of additional animal models, including models in which epilepsy is induced by stroke, a chemoconvulsant (kainic acid), or status epilepticus (11–13). Whether seizures themselves cause the progression in these models is currently under investigation. That said, study of the kindling model clearly demonstrates that recurrent isolated seizures, not simply status epilepticus, are sufficient to produce spontaneous recurrent seizures and destruction of cortical gray matter (6,7). Given the presence of recurrent seizures in a subset of humans with medically refractory MTLE and progressive increase of seizure frequency in animal models (e.g., status epilepticus and stroke), it seems plausible that recurrent seizures per se constitute one factor contributing to the progression of the epileptic state.

SEIZURES: A PATHOLOGICAL FORM OF NEURONAL ACTIVITY

Elucidating the molecular mechanisms by which recurrent seizures promote worsening of the epileptic condition evident as spontaneous recurrent seizures and destruction of cortical gray matter may provide novel targets for drugs aimed at limiting worsening of the condtion in humans and also provide clues to the underlying cellular mechanisms. The recurrent, isolated seizures that cause worsening of seizures and death of cortical neurons in the kindling model consist of an abnormal form of neuronal activity. Thus, the question arises as to how fleeting changes in neuronal activity (i.e., isolated recurrent seizures) produce a lasting change of brain structure and function (i.e., more severe seizures and destruction of neurons). Similar questions are being posed with respect to physiological forms of activity, the idea being that fleeting experiences are associated with fleeting patterns of neuronal activity. For example, how are fleeting visual experiences during development transformed into the lasting structural and functional modifications that underlie normal vision? How are brief experiences transformed into a memory that persists for a lifetime? Gene transcription is one molecular mechanism by which fleeting experiences can be encoded as persistent changes in neuronal structure and function. This "answer," in turn, raises the question as to which particular gene(s) might underlie the lasting modifications of neuronal structure and function that culminate in worsening of the epileptic condition in MTLE.

BRAIN DERIVED NEUROTROPHIC FACTOR: AN ATTRACTIVE CANDIDATE GENE

If gene transcription provides a molecular mechanism underlying worsening of MTLE, what are the features of that particular gene (or genes), the transcription of which might lead to the lasting modifications of neuronal structure and function underlying worsening of MTLE? Important criteria for such a gene include the requirements that its expression is regulated by seizure activity, and that structural and functional consequences of its expression in model systems mimic features of an epileptic brain.

One gene meeting those criteria encodes brain derived neurotrophic factor (BDNF). Yves Barde and colleagues (14) purified BDNF protein from pig brain extracts in their search for a factor that supported the survival and neurite outgrowth of embryonic chick sensory neurons. BDNF was subsequently found to activate a receptor tyrosine kinase named TrkB (15). Packaged in dense core vesicles in axon terminals, BDNF is a 14 kd secreted protein that binds to the ectodomain of TrkB, thereby inducing receptor dimerization, activation of the receptor tyrosine kinase activity, and the phosphorylation of select tyrosines in the cytoplasmic domain – which creates docking sites for adaptor proteins (shc) or enzymes (PLCγ1) that couple these receptors to intracellular signaling cascades. Relatives of BDNF include the other neurotrophins: Nerve growth factor (NGF), Neurotrophin-3 (NT3), and Neurotrophin-4 (NT4). Likewise, relatives of TrkB include two other receptor tyrosine kinases, TrkA and TrkC; NGF serves as the ligand for TrkA, BDNF and NT4 for TrkB, and NT3 for TrkC.

Seizure-regulated expression of BDNF, together with its effects in simplified model systems, make the genes forBDNF and its receptor (TrkB) attractive candidate for promoting worsening of MTLE. Seizures induce dramatic increases of BDNF mRNA and protein expression, in both animal models and humans with epilepsy (16–21). Moreover, activation of TrkB by BDNF produces structural plasticities of the hippocampal dentate granule cells (22) similar to those identified in the epileptic brain (23–27). Moreover, BDNF promotes enhanced efficacy of excitatory synapses connecting principal neurons, a form of long term potentiation (28–36) which is a type of plasticity identified at synapses of animal models of epilepsy (37). BDNF-mediated activation of TrkB can also compromise GABA-mediated inhibition (38).

EVIDENCE IMPLICATING BDNF AND TRKB IN MTLE

A. Animal Models *In Vivo*

Because blood-brain barrier permeable drugs that selectively inhibit the activation of TrkB by BDNF have not been available, elucidating a causal role of BDNF and TrkB signaling in animal models of MTLE has required the development of genetically modified mice. Although mice lacking both *BDNF* alleles in the germline die in the neonatal period, elimination of just one *BDNF* allele results in a striking inhibition of development of kindling (39). An alternative approach utilized "Trk receptor bodies", recombinant proteins that bind and thereby scavenge neurotrophin ligands selectively for either TrkB or its relatives, TrkA and TrkC. Intraventricular infusion of TrkB receptor bodies markedly inhibits the development of kindling in adult rats whereas infusion of TrkA or TrkC receptor bodies has no effect (40). These findings demonstrate that scavenging BDNF *de novo* in the adult brain inhibits kindling development, suggesting that the consequences of absent BDNF during development are not sufficient to explain the impaired kindling found by Kokaia et al (39). Moreover, these findings suggest that the neurotrophin receptor pivotal for seizure progression in this model is TrkB, not TrkA or TrkC. This suggestion was reinforced by the discovery that a conditional deletion of TrkB from subsets of CNS neurons eliminated all behavioral evidence of seizure-induced progression of epilepsy in the kindling model [(41); Figure 1)]. This conditional deletion of TrkB is the sole genetic or pharmacological perturbation known to eliminate all vestiges of behavioral evidence of kindling development. Taken together, these findings provide compelling evidence that TrkB is necessary for seizure-induced progression of epilepsy in the kindling model and suggest that TrkB is activated by BDNF in this condition.

In additional studies, the issue of whether increasing expression of BDNF or TrkB was sufficient to induce hyperexcitability and limbic epilepsy has been addressed. Indeed, intrahippocampal infusion of BDNF, or transgenic overexpression of either BDNF or TrkB in transgenic mice, proved sufficient to increase seizure susceptibility or severity or induce seizures outright (42–45). These findings support the conclusion that enhanced BDNF-mediated activation of TrkB is *sufficient* to induce hyperexcitability and limbic epilepsy. The evidence of both sufficiency and necessity of BDNF and TrkB signaling in these animal models *in vivo* raises the question of whether this signaling pathway may be instructive for seizure-induced progression of MTLE. If so, then seizures themselves would be expected to produce enhanced activation of TrkB.

B. Limbic Seizures Enhance TrkB Activation

The occurrence of enhanced TrkB activation as a consequence of seizures would strengthen the likelihood that signaling activated by TrkB serves an instructive role in seizure-induced progression of MTLE. If seizures induce enhanced activation of TrkB, then elucidating the anatomic locale of this enhancement could pinpoint a specific population of neurons at which to investigate the cellular consequences of the enhanced activation of TrkB. And if seizures induce enhanced activation of TrkB, this would raise the question as to the molecular mechanism by which seizures led to enhanced activation of TrkB *in vivo*.

How does one measure activation of a receptor tyrosine kinase like TrkB? In contrast to ionotropic receptors for glutamate or GABA, the activation of which can be measured with electrophysiological techniques, a commonly used method for measuring activation of receptor tyrosine kinases utilizes antibodies that recognize phosphorylated tyrosines in the cytoplasmic domain of these proteins. Because activation of TrkB involves phosphorylation of specific tyrosine residues in its cytoplasmic domain (46), the availability of antibodies that selectively recognize the phosphorylated form of Trk receptors (pTrk) provides a surrogate measure of TrkB activation in western blot studies of membrane fractions or in immunohistochemical studies. Immunohistochemical evidence of increased TrkB activation, evident as increased pTrk immunoreactivity in the mossy fiber pathway of hippocampus, has been shown following induction of seizures by diverse patterns of electrical stimulation and diverse chemoconvulsants in rats and mice (41,47–49). Interestingly, the biochemical

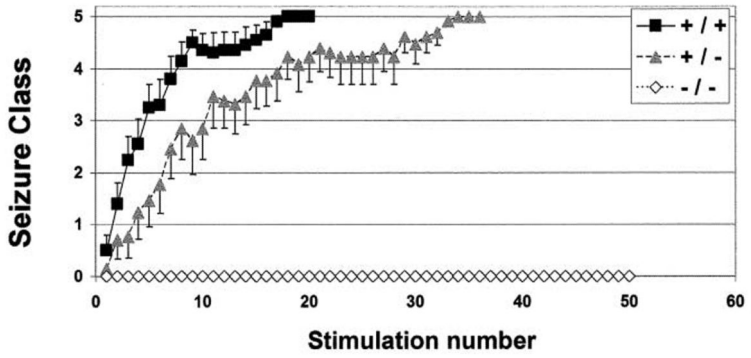

Figure 1. Inhibition of kindling by conditional deletion of TrkB. Kindling was compared between three groups of mice: TrkB$^{-/-}$, TrkB$^{-/+}$ and TrkB$^{+/+}$. Seizure score was measured in response to each kindling stimulation using the Racine scale (Stages 1–5). Seizure score increased progressively with kindling stimulations for TrkB$^{+/+}$ mice but was reduced in TrkB$^{-/+}$ mice and no seizures were elicited in TrkB$^{-/-}$ mice. From (41); reprinted with permission from Cell Press.

and immunohistochemical evidence of TrkB activation is evident beginning several hours after occurrence of seizures and dissipates within one week (47).

C. Potential Cellular Consequences of TrkB Activation Induced By Seizures

The demonstration that seizure-induced progression of epilepsy is inhibited in the TrkB and BDNF mutant mice, together with evidence of enhanced TrkB activation in diverse seizure models, suggest that the cellular consequences of enhanced activation of TrkB may promote progression of MTLE. The anatomic localization of the increased pTrk immunoreactivity to the mossy fiber pathway directed our study of potential cellular consequences of TrkB activation to this locale. Both *ex vivo* and *in vivo* studies of animal models raise the possibility that long-term potentiation (LTP) of excitatory synapses between principal cells may contribute to limbic epileptogenesis (37); that is, potentiation of these synapses may facilitate propagation of seizure activity through synaptically-coupled neuronal populations throughout the limbic system and beyond. In support of this hypothesis, we showed that development of LTP of the synapses made by mossy fiber axons of the dentate granule cells with CA3 pyramidal cells requires TrkB kinase activity (50). Further, study of hippocampal slices isolated from animals following induction of seizures *in vivo* (in the kainic acid model) revealed that the mossy fiber-CA3 synapse had undergone LTP (51). The requirement for TrkB-dependent signaling for LTP of this synapse, together with immunohistochemical evidence of increased TrkB activation in the mossy fiber pathway in sections *ex vivo* from these models [46, 47], suggests that activation of TrkB *in vivo* may contribute to the LTP of this synapse induced by seizures.

The results of these *in vitro* and *ex vivo* electrophysiological studies in animal seizure models are consistent with earlier studies of hippocampal slices isolated from naïve rats; those studies revealed that transient tissue exposure to recombinant BDNF led to potentiation of the mossy fiber-CA3 synapse (52). Potentiation was long-lasting, continuing long after exposure to BDNF, as shown also for BDNF-induced potentiation in area CA1 (32). The effects of BDNF in area CA3 appeared to be specific to the mossy fiber input, because activation of the recurrent collaterals or input from fibers in the fimbria did not exhibit synaptic potentiation. Furthermore, the intrinsic properties of CA3 neurons did not appear to be affected by this treatment (53), and fiber volleys which were also unaffected by BDNF (52). Potentiation was Trk-dependent, as shown by its blockade by the antagonist K252a (52).

Notably, enhanced excitability in models of epilepsy is often accompanied (and likely caused) by both enhanced function of excitatory synapses and impaired function of inhibitory synapses. Might enhanced activation of TrkB also compromise inhibitory function and thereby contribute to the increased excitability seen in limbic epilepsy? One interesting possibility is that enhanced TrkB activation reduces expression of the K-Cl

cotransporter, KCC2, resulting in accumulation of $[Cl^-]_i$ and a shift of E_{GABA} in a depolarizing direction (54). Direct study of human epileptic tissue (55,56), as well as extensive study of diverse *in vivo* and *in vitro* models (54,57–61), suggest that reduced expression of KCC2 and resulting accumulation of $[Cl^-]_i$ is an important molecular and cellular mechanism contributing to limbic epilepsy. Further, *in vitro* studies demonstrate that TrkB-mediated activation can suppress KCC2 expression (54,57). Whether TrkB-mediated activation is responsible for reductions of KCC2 expression described in the kindling and pilocarpine models (57,60) *in vivo* is unclear.

WHAT IS THE MOLECULAR MECHANISM MEDIATING TRKB ACTIVATION BY SEIZURES *IN VIVO*?

The localization of the increased p-Trk immunoreactivity to the mossy fiber pathway provided us with the opportunity to examine the molecular mechanism by which seizures induced the increased p-Trk immunoreactivity. The striking seizure-induced increases of BDNF immunoreactivity in the mossy fibers occurred with a time course similar to that of increased p-Trk immunoreactivity, thus supporting the idea that BDNF was responsible for the increase in p-Trk immunoreactivity. Unexpectedly, seizures induced an increased p-Trk immunoreactivity in the mossy fiber pathway in conditional BDNF null mutant mice similar to that seen in wild type control mice (41). What mediated the increased TrkB activation in the mossy fiber pathway following seizures in the *BDNF* –/– mice? The increased expression of NT-3 protein in the *BDNF* –/– mice is an interesting possibility, both because of NT-3's ability to activate TrkB (15,62,63) and the localization of NT-3 to the dentate granule cells (64,65), whose mossy fiber axons coincide with the spatial distribution of the activated TrkB. Alternatively, transactivation of TrkB by zinc may contribute. "Transactivation" refers to the process whereby a given receptor and its downstream signaling is activated by a stimulus that does not interact directly with the receptor (66), a mechanism distinct from activation of TrkB by neurotrophins. The seizure-induced activation of TrkB is localized to the mossy fiber pathway (67–69) and the mossy fiber axons contain the highest concentration of zinc in mammalian forebrain (70). Zinc is packaged in synaptic vesicles together with glutamate and is released with glutamate by physiological stimulation (71). We demonstratted that zinc transactivates TrkB by a neurotrophin-independent and Src-dependent mechanism that is regulated by neuronal activity (50). One functional consequence of zinc-mediated transactivation of TrkB is LTP of the mossy fiber-CA3 pyramid synapse. While zinc can transactivate TrkB *in vitro*, whether endogenous zinc contributes to TrkB activation in the hippocampal mossy fiber pathway following seizures *in vivo* awaits further study.

THE POTENTIAL ROLE OF BDNF IN CATAMENIAL EPILEPSY

The discussion above provides compelling arguments for a role of BDNF and TrkB in limbic epileptogenesis and MTLE. In addition, BDNF and TrkB signaling can potentially explain some questions that have puzzled scientists who study epilepsy, such as the reason why a subset of patients appear to become progressively worse, either because they develop pharmacoresistance, neuroimaging shows progressive structural deterioration, or mood and cognitive side effects becomes increasingly severe. Another common question - albeit one that seems very different - is the reason why the reproductive endocrine system has such powerful effects on seizures. Below we discuss this question as it relates to BDNF, and suggest that although progression in MTLE and the effects of reproductive steroids on seizures seem very different, both may be explained, at least in part, by the effects of BDNF.

One of the reasons why the relationship between reproductive hormones and seizures has remained unclear is that effects of estrogen, progesterone, and testosterone, the major reproductive steroid hormones, are usually inconsistent. The reasons for the lack of consistency are unclear, and may be based in biological complexity, or there simply could be an appearance of inconsistency because of differences in experimental procedures across studies (72).

The clinical observations that suggest a role of reproductive steroids in epilepsy are diverse. They include reports of changes in seizures at times of life when reproductive status is altered, such as puberty, when epilepsy is often diagnosed for the first time (73). In pregnancy, or at menopause, other times of life when large fluctuations in reproductive steroids occur, there also are changes in seizure severity in women with epilepsy (74,75), although it is not universal. Other clinical data that support an influence of reproductive hormones on epilepsy are based on studies which have evaluated circulating levels of specific reproductive hormones, such as estrogen and progesterone, and shown that when these levels fluctuate, seizures often fluctuate in severity (72,76–79).

Here we address the effects of reproductive steroids on seizures by focusing on seizures during the menstrual cycle, a condition that is easier to study than puberty or menopause because it occurs at a relatively stable time of life (adulthood) and is relatively short in length (28 days). In addition, menstrual cycles are repetitive, providing scientific advantages because measures can be repeated. However, studies of seizures during the menstrual cycle present some challenges. One problem is the ability to distinguish the effects of hormones like estrogen and progesterone from other changes that occur during the menstrual cycle, such as changes in luteinizing hormone or follicle stimulating hormone. Fluid retention, which often occurs during the perimenstrual period, can have effects on seizures that are independent of reproductive steroid levels (80–82). In addition, there are potential confounds of seizures in studies of the menstrual cycle in women with epilepsy, because there can be acute effects of a seizure on the endocrine system (even a single seizure), such as elevation in prolactin (82). Effects of repeated seizures also have consequences for the endocrine system. Long-term, chronic seizures appear to adversely affect reproductive function, such as irregular or anovulatory cycles and polycystic ovarian syndrome (PCOS) (74,83). These adverse effects have been suggested to be due to AEDs such as valproic acid, but there is evidence that seizures also contribute to the disruption of menstrual cycles and PCOS (84,85). A strong argument for a role of chronic seizures in reproductive dysfunction (including irregular cycles and PCOS) instead of a role of AEDs, is that laboratory animals show signs of acyclicity and PCOS after repeated seizures - without ever being treated with AEDs (85–89). Another challenge to research is that the endocrine systems of women and laboratory rodents are very different. The differences are exemplified by a comparison of the ovarian cycle of women and the laboratory rat. As shown in Figure 2A, the rat cycle (estrous cycle) is only 4 days, in contrast to the 28-day menstrual cycle in women. In addition, there is primarily one surge in estrogen during the estrous cycle in rats that occurs just before ovulation, but in women, there is a preovulatory surge as well as a secondary increase in estrogen between day 14 and 28, the luteal phase (Figure 2).

CATAMENIAL EPILEPSY: DEFINITION AND POTENTIAL MECHANISMS

Catamenial epilepsy refers to seizures that increase in frequency or severity at specific stages of the menstrual cycle (90), and has been known for a long time. One of the first descriptions was published by Gowers in the same monograph that is discussed in the first section of this chapter (1). In the last decades, as the effects of hormones on excitability became better documented, there has been a more focused discussion about hormone-sensitive seizures. The ensuing clinical research studies that defined the incidence of catamenial epilepsy have not always been in agreement, with many investigators not completely convinced that catamenial epilepsy is a robust, reliable phenomenon (91) and others reporting, in contrast, a substantial prevalence, approximately one-third of women with epilepsy (92).

Bäckstrom (93) was one of the first to document seizures in women that varied during the menstrual cycle. Both the seizures and response to AEDs seemed to fluctuate, and did so mostly at two times of the menstrual cycle: 1) mid-cycle, when ovulation occurs, and 2) at the end of the cycle, when menstruation begins. The times when seizures worsened were not exactly at the time of ovulation or the onset of menses, leading to the terms “periovulatory” and “perimenstrual” to describe the two patterns.

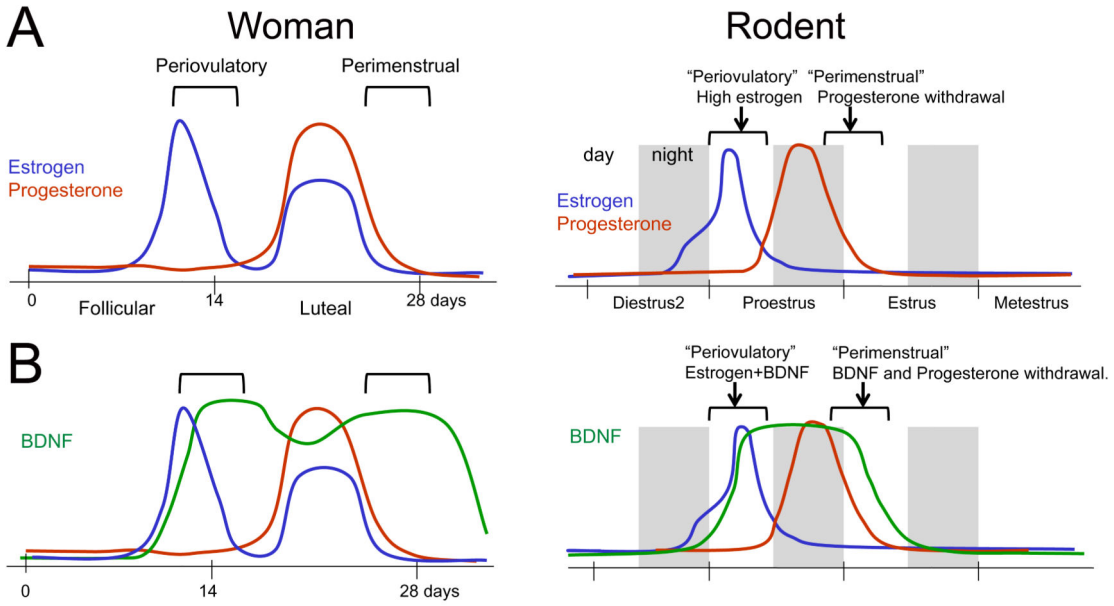

Figure 2. Explanations for catamenial epilepsy. Top: The estrogen/progesterone hypothesis for catamenial epilepsy is shown schematically. The changes in serum estrogen and progesterone levels during the ovarian cycle are diagrammed for the rat (A) and woman (B). In the rat, there is a four day cycle called the estrous cycle. In women, the 28-day cycle is divided into a follicular and luteal phase. In catamenial epilepsy, the periovulatory and perimenstrual periods are typically when seizures worsen; the analogous times are marked for the rodent and human cycles (72). One of the most common hypotheses to explain catamenial epilepsy is based on the idea that estrogen is proconvulsant and progesterone has the opposite effect (72, 77). In addition, when progesterone levels fall dramatically at the end of the luteal phase, increased excitability has been demonstrated, and this contributes to perimenstrual seizure exacerbation (72, 76, 77, 78, 145, 146).

Bottom: An alternate hypothesis for catamenial epilepsy based on the role of BDNF in actions of estrogen and progesterone. A) The rise in hippocampal BDNF during the estrous cycle in the female rat is shown schematically, based on immunocytochemistry (97), and illustrates a long-lasting elevation in BDNF after the preovulatory surge in estrogen. B) Based on the rodent data, a schematic is shown that illustrates the predicted rise in BDNF levels that would occur in women, i.e., a long-lasting rise in BDNF following the preovulatory rise in serum estrogen levels. Because estrogen also rises during the luteal phase, BDNF could remain elevated for the entire luteal phase and the perimenstrual period. This prediction has support from measurements of serum BDNF in women, which is high during the luteal phase relative to the follicular phase (111). Note that the times when BDNF is elevated and progesterone is low correspond well to the periovulatory and perimenstrual periods, in both rat and woman, providing an alternative hypothesis for catamenial epilepsy.

Bäckstrom (93) suggested that the fluctuations in seizures were due to changes in serum levels of estrogen and progesterone, because of the large increase in circulating estrogen concentration that occurs just before ovulation, and a dramatic fall in progesterone levels at the end of the menstrual cycle (Figure 2A). Bäckstrom suggested that the relative levels of estrogen and progesterone (the estrogen/progesterone "ratio") helped explain the rise and fall in seizures: high ratios explaining seizure exacerbation, and low ratios correlating with times when seizures were controlled by AEDs or were less severe/less frequent.

Herzog and colleagues (90) described three patterns of catamenial epilepsy: 1) seizures that worsen during the periovulatory period, 2) seizures that worsen during the perimenstrual period, and 3) seizures that worsen during anovulatory cycles when there is a failure of luteal rise in progesterone. The third type of seizure pattern helped describe some women with epilepsy who developed irregular cycles or reproductive dysfunction in the course of epilepsy, and experienced more severe or frequent seizures. Herzog and colleagues (90) echoed the suggestion of Bäckstrom, that high estrogen levels were responsible for periovulatory seizures and the dramatic fall in progesterone late in the menstrual cycle caused perimenstrual seizure exacerbation. Furthermore, anovulatory cycles, associated with exacerbation of seizures, were attributed to low levels of progesterone (90).

The basis for the idea that estrogen and progesterone levels explain seizure frequency was based on an emerging understanding of estrogen and progesterone actions in the brain at the time. To a large extent, experimental data suggested that estrogen was excitatory, and some investigators showed it facilitated seizures or was "proconvulsant" (72). In contrast, progesterone appeared to be inhibitory, an effect mediated by its metabolite allopregnanolone (see below). As a result, progesterone or allopregnanolone were considered "anticonvulsant." These ideas were attractive as a parsimonious way to explain clinical data, and were consistent with neuroendocrinological findings outside of the field of epilepsy. However, the actions of estrogen and progesterone can also be potentially explained by their effects on BDNF.

ALTERNATE EXPLANATIONS FOR CATAMENIAL EPILEPSY BASED ON THE INTERPLAY BETWEEN ESTROGEN, PROGESTERONE, AND BDNF

A. The Role of BDNF in the Actions of Estrogen

It has been known for some time that estrogen targets growth factors, and in early life this interaction is thought to be critical for appropriate neurodevelopment (94). However, it was only recently suggested that estrogen may target growth factors in the brain, and specifically the neurotrophins (94). In 1995, the link between estrogen and BDNF in the brain became better defined when Sohrabji and colleagues identified an estrogen response-like element on the gene for BDNF, and showed that ovariectomy of adult female rats reduced BDNF levels in the brain, and estrogen treatment reversed the effect [(95); see also (96)]. These studies raised the following question: do physiological fluctuations in estrogen also induce BDNF synthesis? In addition, where in the brain would estrogen-induced BDNF synthesis occur? One would think that it would occur wherever BDNF protein synthesis normally occurs, such as the mossy fiber axons of dentate gyrus granule cells, one of the areas of the brain where BDNF protein expression is most robust (16, 99, 100).

To answer these questions, intact female rats were compared at various stages of the estrous cycle. BDNF protein expression, evaluated with immunocytochemistry using hippocampal sections, increased in the mossy fiber pathway on proestrous morning, the time when serum estradiol peaks during the estrous cycle (97). These data supported the hypothesis that periodic increases in circulating estradiol during the normal estrous cycle led to an increase in BDNF protein content in areas of the brain where it normally was synthesized.

Remarkably, the peak of BDNF levels in the mossy fiber pathway was actually not on proestrous morning, when serum concentrations of estradiol are highest, but the next day, long after serum levels of estradiol return to baseline in the rat (97). Therefore, BDNF levels were increased with a time course that outlasted the preovulatory surge in serum estradiol concentration. Furthermore, BDNF levels were highest at the time of the estrous cycle that is analogous to the perimenstrual period, when it is most common for seizures to worsen in women with epilepsy (98).

These data suggested a potential explanation for catamenial seizure exacerbation: elevated BDNF levels increase seizure susceptibility. The locations where BDNF increased supported that idea, because BDNF protein was elevated in areas that are thought to be important in seizure generation, such as hippocampus. In addition, the amygdala showed an increase in BDNF protein by immunocytochemistry (Scharfman et al., unpublished). It is especially interesting that the areas where BDNF was increased contribute to TLE, because catamenial epilepsy appears to be most common in TLE (98).

The increase in BDNF levels that occurred in the mossy fiber pathway of female rats provided an opportunity to test the hypothesis that increased levels of BDNF exert functional effects that are consistent with a pro-convulsant action (16,99,100). Therefore, we made recordings in hippocampal slices and compared slices that were prepared from female rats during different estrous cycle stages. We found that the increase in mossy fiber

BDNF was correlated with an increase in mossy fiber transmission. The nature of the increase in mossy fiber transmission was interesting because it suggested hyperexcitability. However, this type of hyperexcitability was not simulated by perfusion of slices with convulsants, such as $GABA_A$ receptor antagonists, so it seemed to be a novel form of hyperexcitability (53). Most convulsants, such as the $GABA_A$ receptor antagonist bicuculline, induce area CA3 population discharges that occur at spontaneously and rhythmically. In contrast, female rats with elevated mossy fiber BDNF protein did not demonstrate spontaneous burst discharges in area CA3 (or any other area of the slice). Instead, hyperexcitability was manifested in a different way. Stimulation of the mossy fibers at 1 Hz using pairs of stimuli (40 msec interstimulus interval, at 50% maximal stimulus strength) produced multiple population spikes (after each stimulus) with only 3–6 pairs of stimuli required (52,53,97). The population spikes that followed each stimulus occurred in trains with approximately 10–20 msec between each population spike, and the entire train did not last more than 100 msec. Therefore, the hyperexcitability was different from the type of synchronized population bursts that occur in area CA3 after bicuculline exposure (53). Spreading depression often followed the evoked trains of population spikes that were elicited by 1 Hz stimulation of the mossy fibers (52,53,97). These data were interesting because both the pattern of population spike trains after stimulation and the spreading depression episodes were also observed after exposure of male rat slices to to recombinant BDNF (52). However, the female rat slices had no exposure to recombinant BDNF. All of the effects that were recorded in slices from female rats at cycle stages with high mossy fiber BDNF protein expression were similar to those effects that had been previously described in slices from male rats that had been exposed to recombinant BDNF (52,97). Importantly, the effects that were evident in slices from female and male rats were blocked by K252a, a Trk receptor antagonist, consistent with the interpretation that BDNF was responsible (97).

These data suggested that during every estrous cycle, the rise in serum levels of estradiol triggers BDNF synthesis in pathways like the mossy fibers, and the net effect is an increased susceptibility to epileptiform activity. Therefore, it seemed plausible that actions of estrogen that increased seizure susceptibility in catamenial epilepsy are mediated by BDNF. Actions of estrogen could explain both periovulatory seizure exacerbation as well as the increase in seizures during the perimenstrual period because BDNF protein is elevated in the rat at the analogous times of the estrous cycle, i.e., proestrous morning and estrous morning. Furthermore, Trk-dependent epileptiform activity was evoked by mossy fiber stimulation at both proestrous and estrous mornings. The experiments in female rats also suggested a potential reason why perimenstrual seizures might be more common in women than periovulatory seizures: BDNF levels were highest in the female rat at the time that is analogous to the perimenstrual period, estrous morning, and stimulus-evoked epileptiform activity in the female rat was most severe at that time (97).

There are many neuromodulators that are altered on proestrous morning in the female rat, not only BDNF. For example, there are changes in norepinephrine and corticosterone levels (101,102). Therefore, it was important to use another approach so that we could dissociate the effects of estrogen from the potential effects of norepinephrine and corticosterone. Therefore, ovariectomized rats were treated with a series of injections that simulates the rise in 17β-estradiol (estradiol) during the estrous cycle (103). These experiments demonstrated that estradiol treatment *per se* could reproduce the effects observed in the intact rat, and supported the hypothesis that estradiol was responsible for the increase in mossy fiber BDNF and increased mossy fiber transmission in the intact rat. Together these experiments suggest new mechanisms that mediate the effects of estrogen in catamenial epilepsy. Estrogen may increase seizure susceptibility indirectly, by inducing BDNF synthesis. In turn, BDNF exerts effects that facilitate seizures.

It is important to note that the effects of estrogen on BDNF may not be mediated by the estrogen-response element on the BDNF gene. It has been suggested that estrogen acts on GABAergic neurons to cause disinhibition (104–107). Therefore, BDNF levels may increase because of activity-dependent expression (107).

The reason why BDNF levels remain high long after estrogen levels return to normal during the estrous cycle is currently unclear. One contributing factor to the long-lasting nature of increased BDNF expression may be

effects of progesterone, which rises immediately after estrogen during the estrous cycle (Figure 2A), and therefore is increased at a time that is well-suited for a modulatory action. Although progesterone is commonly thought to counter-act estrogen action, the actions of progesterone during the estrous cycle can facilitate estrogen action, at least with respect to reproductive behavior (72,120). The experiments that have addressed the effects of progesterone on BDNF, however, have produced variable results. One study showed that BDNF was increased by progesterone, acting at progesterone receptors (108). Another study showed that ovariectomized animals treated with estrogen exhibited increased BDNF expression, and a subsequent injection of progesterone inhibited that effect (109). Other studies have found little effect of progesterone on BDNF (110).

Importantly, evaluation of BDNF levels in women suggest that cycle-dependent changes in serum BDNF in women are similar to BDNF levels in hippocampus of female rats. Thus, analysis of serum BDNF in normal women showed that BDNF levels were high at ovulation and during the luteal phase relative to the follicular phase (111). Although BDNF levels in brain were not studied, the data from serum samples is consistent with the idea that the ovulatory and luteal rise in estrogen in women is associated with an increase in BDNF levels in the brain.

In light of the data from the female rat, one explanation for catamenial epilepsy would be that estrogen and progesterone modulate BDNF synthesis, with estrogen and progesterone potentially increasing BDNF synthesis, and allopregnanolone keeping any proconvulsant effects in check. This hypothesis would explain the three types of catamenial epilepsy suggested by Herzog and colleagues as shown in Figure 2B. During the periovulatory period, proconvulsant effects of BDNF would emerge because of an increase in BDNF synthesis induced by the preovulatory surge in estrogen. During the luteal phase, high levels of allopregnanolone would be likely to keep the effects of elevated BDNF, i.e., increased predisposition for seizures, in check. However, during the perimenstrual period when progesterone levels fall, seizure exacerbation would be predicted because BDNF levels would still be high, but the effects of BDNF would no longer be counterbalanced by enhanced inhibition (Figure 2). This view suggests that estrogen and progesterone are modulators of BDNF, and do not cause the fluctuation in seizures during the menstrual cycle by direct effects.

A key component of this hypothesis is the argument that BDNF has effects that facilitate seizures, and can explain many of the actions of estrogen. There is a great deal of data to support this idea. Effects of estrogen are mainly inferred from studies of the major bioactive form of estrogen, 17β-estradiol (estradiol), which is produced in the periphery (primarily in the ovaries), and also can be produced centrally from cholesterol metabolism. The effects of estradiol are extremely diverse both in and outside the CNS, but they appear to be mediated entirely by three receptors: a membrane-bound receptor (mER) and two types of receptors that can migrate to the nucleus (nuclear receptors; ERα and ERβ) and act on target genes.

During the 1960s and 1970s, investigators showed that estradiol increases excitatory (glutamatergic) transmission, and some of the data suggested that the facilitation of glutamatergic transmission was strong enough to lead to seizures (113,114). One of the first studies that supported this view used a bolus of estradiol applied directly to the cortex in anesthetized cats, and found that the cortical EEG increased, similar to a seizure (113). Since that time, estradiol has been shown to produce many effects in the brain. Almost all of them are consistent with a net excitatory effect. For example, estradiol increases glutamatergic transmission (114), facilitates LTP (114,115), and induces dendritic spine growth (116). The increase in glutamatergic transmission and LTP is potentially mediated by several mechanisms, including actions that are presynaptic as well as postsynaptic (117, 118)

Interestingly, many of the effects of estradiol can also be induced by BDNF (119,120). For example, exposure of hippocampal slices to recombinant BDNF potentiates glutamatergic transmission (32, 52, 53), and BDNF is required for LTP in hippocampus (33,35,50,121). BDNF also has potent effects on NMDA receptors and dendritic spine morphology, like estradiol, although the effects on spines may not be identical to those that have been reported for estradiol (122). Estradiol also increases the rate of postnatal neurogenesis (123), which is an

effect of BDNF as well (124). Estradiol decreases GABAergic transmission, by decreasing levels of the synthetic enzyme for GABA, glutamic acid decarboxylase [(GAD);(125)] and via other mechanisms (104,126); BDNF can also reduce GABAergic inhibition, although a specific action on GAD has not been identified (38,127,128). Studies of BDNF *in vivo* in the context of seizures and epilepsy demonstrated it is potentially proconvulsant (as discussed above). Therefore, the actions of estrogen could be mediated, at least in part, by BDNF.

The time that is required for estradiol to exert its effects - relative to the time required for BDNF-dependent effects - is important to consider if one is to argue that BDNF contributes to the effects of estrogen during the menstrual cycle. Although the exact timing of estrogen and BDNF actions during the ovarian cycle are not clear in rodents or in women, from what is known it is possible that BDNF mediates all actions of estrogen. Thus, even the "rapid" effects of estrogen in rodents during the periovulatory period that are detected 12–18 hrs after the start of the preovulatory surge in estrogen can be explained by estrogen-induced BDNF synthesis because 12–18 hrs is long enough for induction of protein synthesis.

Importantly, the effects of estradiol do not seem to be universally "convulsant" [for review, see (72)]. One explanation is that estrogen has a pro-convulsant effect because of its induction of BDNF synthesis, and estrogen also exerts an effect that is indirectly anticonvulsant because it leads to an increase in levels of neuropeptide Y (NPY), which has effects that are usually anticonvulsant (129,130). The effect of estrogen on NPY levels could be mediated by BDNF, because BDNF induces NPY synthesis following TrkB activation (131–134). Therefore, some of the reasons estrogen is convulsant could be due to its effects on BDNF synthesis, and some of the reasons it is not convulsant could also be due to BDNF-mediated effects (see also (135)).

The actions of estrogen that are protective are also relevant to a discussion of epilepsy, particularly TLE, because limbic pathology (e.g., neuronal loss) is a characteristic of TLE that appears to be influenced by estradiol. However, effects of estradiol on neuronal damage after experimental seizures seem to vary from study to study (119,120). Interestingly, the same is true for BDNF. BDNF can exacerbate toxicity to convulsants such as kainic acid in culture (136), similar to estradiol, but it also appears to protect neurons against excitotoxicity in other experiments, which is also similar to some studies of the effects of estradiol (137). One explanation that has been used to explain the varied effects of estradiol is that high doses or chronic treatment can downregulate estrogen receptors (ER) (138–140; see also (141). The same explanation has been used to explain the varied effects of BDNF: high doses decrease TrkB receptors at the plasma membrane (45).

B. The Role of BDNF in the Actions of Progesterone

If the effects of estrogen on seizures can potentially be explained, at least in part, by BDNF, is the same true for progesterone? Many would think not, because the effects of progesterone on seizures that many investigators consider to be most robust are mediated by allopregnanolone, which binds directly to the $GABA_A$ receptor. However, the effects of BDNF may still play a role here, because BDNF can alter several aspects of GABAergic transmission.

Effects of progesterone are mediated by membrane and nuclear receptors, analogous to estrogen. Whereas actions of estrogens can be mediated by different forms (estrone, estriol, estradiol), the effects of progesterone are due to progesterone itself, as well as its metabolites. The effects of progesterone at progesterone receptors (PR) have effects that alter excitability (142,143), but the most is known about the metabolite allopregnanolone. Allopregnanolone is an allosteric modulator of the $GABA_A$ receptor; when allopregnanolone binds, the effects of GABA at $GABA_A$ receptors are potentiated (144,145). Unlike effects of estradiol and BDNF, which seem to be very sensitive to experimental conditions, the anticonvulsant effects of allopregnanolone are very consistent from one experimental paradigm to the next (76).

The available clinical data support the view that allopregnanolone controls seizures during the luteal phase of the menstrual cycle in women because allopregnanolone levels rise at that time. In addition, increased seizure

severity during the periovulatory, perimenstrual and anovulatory cycles can be explained by low levels of allopregnanolone. Therefore, progesterone, or other drugs that simulate neurosteroids acting at $GABA_A$ receptors, such as ganaloxone, have been suggested as AEDs (146).

Although fluctuations in allopregnanolone levels can provide an explanation for the three types of catamenial epilepsy, there may be an influence of BDNF on the effects of allopregnanolone that is important to consider. For example, the α2, β2/3 and γ2 subunits of $GABA_A$ receptors are downregulated when neurons are exposed to BDNF in culture, which increases excitability (147). However, cell surface expression of δ subunits increase in response to BDNF (149), which should enhance the effects of allopregnanolone, not diminish them, because δ subunits typically facilitate actions of allopregnanolone at $GABA_A$ receptors (149). The effects of BDNF on $GABA_A$ receptors are complex because it appears that BDNF does not only modulate receptor subunit expression, but also can influence GABAergic transmission by increasing GABAergic synapse density (150) and modulating GABA release (151) and KCC2 expression (152).

Perimenstrual seizure exacerbation has been explained not only by low levels of allopregnanolone, but the rapid reduction in progesterone levels at the end of the ovarian cycle (146). This condition of "progesterone withdrawal" is associated with seizure susceptibility, which has been explained by an increase in α4 subunits of $GABA_A$ receptors (153). BDNF has been shown to increase α4 expression by activating the transcription factor Egr3 (154). Therefore, the elevation of BDNF during the luteal phase of the menstrual cycle could lead to α4 upregulation by the end of the luteal phase, explaining the increase in seizure susceptibility during the perimenstrual period. BDNF may also contribute to progesterone "withdrawal" in other ways. For example, falling levels of allopregnanolone at the end of the menstrual cycle would be likely to cause disinhibition, which could lead to an increase in BDNF levels because BDNF synthesis is activity-dependent. An increase in BDNF protein would increase excitability by the facilitatory effects of BDNF on synaptic transmission.

BDNF may have other effects that increase excitability by actions on $GABA_A$ receptor subunits besides δ or α4 subunits. For example, it has been shown that upregulation of BDNF decreases α1 subunits (155). This is important because of the evidence, in an animal model of epilepsy, that increasing α1 receptors reduces seizures (156).

SUMMARY

Actions of estrogen and progesterone have been used to explain the changes in seizure frequency or severity in women with catamenial epilepsy. An alternative hypothesis is that BDNF is responsible, because estrogen causes an increase in BDNF expression that can have both acute effects on excitability, as well as delayed, indirect effects by changing GABAergic transmission and $GABA_A$ receptors. Allopregnanolone may hold many of the excitatory effects in check during the luteal phase, but two times of the cycle may be unprotected, the periovulatory and perimenstrual phase. This hypothesis helps explain why progesterone therapy may not always be efficacious in catamenial epilepsy, and suggests that control of BDNF would be a logical complementary strategy.

CONCLUDING REMARKS

The evidence from diverse methods, and diverse animal models, strongly suggests that BDNF contributes to epilepsy, and does so in many ways. In acute seizures, BDNF is likely to play a role because of its rapid actions at many excitatory synapses, and possibly inhibitory synapses. In epileptogenesis, BDNF appears to be a part of a cascade that initiates - and then perpetuates - the process of epileptogenesis. The activity-dependence of BDNF and its specific expression in parts of the brain that regulate seizure susceptibility are two of many specific characteristics of BDNF and TrkB that are likely to make it so influential in epileptogenesis. However, the role of BDNF is not only important in acute seizures and epileptogenesis, but it is also likely to be important in chronic epilepsy, where factors that trigger seizures, such as fluctuations in gonadal hormones, may do so because, at

least in part, they increase BDNF synthesis. In light of the multitude of "proconvulsant" effects of BDNF, the molecular mechanisms that control BDNF synthesis, and molecular mechanisms of TrkB signaling, are attractive targets for anticonvulsant and anti-epileptogenic drug development.

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