HHS Public Access

Author manuscript

Neurosci Lett. Author manuscript; available in PMC 2022 April 17.

Published in final edited form as:

Neurosci Lett. 2021 April 17; 750: 135753. doi:10.1016/j.neulet.2021.135753.

Molecular mechanisms of sex differences in epilepsy and seizure susceptibility in chemical, genetic and acquired epileptogenesis

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Abstract

This article provides a succinct overview of sex differences in epilepsy and putative molecular mechanisms underlying sex differences in seizure susceptibility in chemical, genetic and acquired epileptogenesis. The susceptibility to excitability episodes and occurrence of epileptic seizures are generally higher in men than women. The precise molecular mechanisms remain unclear, but differences in regional morphology and neural circuits in men and women may explain differential vulnerability to seizures and epileptogenic cascades. Changes in seizure sensitivity are due to steroid hormones, including fluctuations in neurosteroids as well as neuroplasticity in their receptor signaling systems. Other potential neurobiological basis for sex differences in epilepsies include differences in brain development, neurogenesis, neuronal chloride homeostasis, and neurotrophic and glial responses. In catamenial epilepsy, a gender-specific neuroendocrine condition, epileptic seizures are most often clustered around a specific menstrual period in adult women. A deeper understanding of the molecular and neural network basis of sex differences in seizures and response to antiepileptic drugs is highly warranted for designing effective, sex-specific therapies for epilepsy, epileptogenesis and seizure disorders.

Keywords

Epilepsy; Epileptogenesis; Estrogen; Neurosteroid; Progesterone; Sex difference; Seizure

1. Introduction

Epilepsy is a chronic neurological disorder characterized by repeated, often debilitating seizures that can result in brain damage, substantial bodily injury, and sometimes death. Numerous subtypes of epilepsies exist, with each of them involving network ensemble

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Declaration of Competing Interest

Nothing to declare.

hyperexcitability and synchrony as a result of dysfunctional neuronal mechanisms. In the United States alone, roughly 3.4 million people suffer from epilepsy, and many of these individuals endure significant socioeconomic burdens as a result of their diagnosis [1,2]. Despite recent advancements in neurology and pharmacology, more than 30% of epileptic patients experience uncontrollable seizures [3,4]. These epilepsies are said to be refractory and do not respond to current antiepileptic drugs (AEDs). Therefore, there is an urgent need for novel pharmaceutical therapies for epilepsy and other related seizure disorders.

The process of developing epilepsy, referred to as epileptogenesis, can be influenced by a myriad of factors. Of them, differences related to biological sex are among the most apparent [5]. There is a disproportionate amount of epilepsy research centered on male individuals. Although greater focus has begun shifting to the relationship between biological sex and epilepsy, there are still gaps in our understanding of sex differences in epilepsy disorders. Epileptic seizures occur randomly in most epileptic men and women. However, seizures are known to occur predictably in women suffering from catamenial epilepsy. Exploring this trend may further increase our knowledge of the mechanisms underlying sex differences in epilepsy. This would then allow us to develop more effective therapies to improve the quality of life for epileptic individuals [6,7]. This article provides a concise overview of sex differences in the epilepsies and discusses potential mechanisms underlying differential seizure susceptibility in epileptic men and women.

2. Sex differences in the epilepsies

2.1. Diagnostic trends

Sex differences in epilepsy are abundant, existing across the gamut of epilepsy syndromes. The extent of these differences varies between specific seizure disorders and is heavily influenced by age-related factors. Women are more frequently diagnosed with idiopathic generalized epilepsies than men [8,9]. In this context, *idiopathic* describes forms of epilepsy which are genetically based. Women are also more commonly diagnosed with cryptogenic localization-related epilepsies, with *cryptogenic* describing epilepsies without obvious causes [10]. In contrast, men are diagnosed more frequently with localization-related symptomatic epilepsies and injury-induced epilepsies [10,11]. More information regarding diagnostic trends in various epilepsy syndromes are listed in Table 1.

There is significant data showing that males experience a higher incidence of epilepsy and thus have an increased risk of developing epilepsy over the course of their lives [12–15). However, sociological factors may influence this trend. There is evidence which suggests that more women than men may attempt to conceal their epilepsy diagnosis in certain countries where epilepsy is heavily stigmatized [16,17].

2.2. Cerebral connectivity and temporal lobe epilepsy

Sexual dimorphism with respect to cerebral connectivity is evident from birth to old age [24]. Studies indicate that the male brain is better equipped to handle intrahemispheric neuronal communication due to a higher abundance of white matter connections between cortical regions [24,25]. In contrast, the female brain exhibits greater interhemispheric

connectivity and local clustering [24–26]. This discrepancy has been described in both the adolescent and adult brain and may partly explain why more women than men are diagnosed with idiopathic generalized epilepsies [8,26,27].

Variations in cerebral connectivity also exist abundantly within the limbic system and are therefore relevant to temporal lobe epilepsy (TLE) [24] (Fig.1). TLE is among the most common forms of epilepsy and is characterized by spontaneous focal seizures originating from within the limbic system [28]. These seizures are often accompanied by impaired awareness and syncope that differ in extent and nature between the sexes [28]. For example, auras are abnormal sensations which precede seizures and are often experienced by individuals with TLE. Women are known to exhibit these auras more commonly than males, although the exact mechanism by which this occurs is unclear [29]. Differences are also seen in the lateralization and generalization of seizures and may be related to differential connectivity within the limbic system (Fig.1). [29]. The typical male brain has a larger amygdala and thalamus than its female counterpart, while the female brain contains a larger hippocampus, caudate nuclei, regional gray matter, and cortices [25,24]. Within the amygdala, men have been shown to have better right-sided connectivity while women have more left-sided neuronal connections [30,31]. Taken together, these structural variations within the limbic system suggest that sex-differences in the epilepsies may be partly explained by underlying, sex-based variations in functional connectivity.

2.3 The relationship between epilepsy and other neurological disorders

Not only are the manifestations of epilepsy disorders affected by biological sex, but they are also influenced by several other neurodegenerative disorders such as stroke, depression, and TBI, all of which have been shown to increase the incidence risk of epilepsy [32]. However, epilepsy is not only affected by concomitant neurological conditions but can affect these conditions as well. One such example is dementia. It is well-documented that individuals suffering from dementia are at a higher risk for developing epilepsy. Yet, pre-existing long-term epilepsy places an individual at higher risk for developing dementia [33,34]. A dementia of particular significance is Alzheimer's disease, as a recent study has discovered via transcriptome sequencing that Alzheimer's disease and epilepsy share common pathogenesis pathways [35].

3. Potential molecular mechanisms of sex differences in epilepsy

A variety of mechanisms have been proposed to account for sex-based differences in the epilepsies and seizure sensitivity [6]. Such factors include body weight, steroid hormones, cytochrome P450 activity, neurotransmitter systems, and sexually dimorphic neuronal networks in the brain [7,36–38]. Of these, the impact of steroid hormones and endogenous neurosteroids on neuronal excitability and seizure susceptibility are among the most widely investigated [7,39–43].

3.1. Neurosteroids

The influence of neurosteroids on seizure susceptibility and epileptogenesis have been gaining recognition in recent years. Neurosteroids such as allopregnanolone (AP,

brexanolone) and androstanediol mediate the activity of $GABA_A$ receptors [44]. This occurs throughout the brain and produces significant neuronal inhibition [39]. Availability of steroid hormones such as progesterone and testosterone affects the production of neurosteroids in the brain. Sex-based differences in the endocrine system therefore play a role in producing inhibitory neurosteroids. There have not been any studies to suggest that reduced levels of neurosteroids can result in epileptogenesis. However, the striking influence that neurosteroids have on neuronal inhibition serves as a likely basis for sex differences in epilepsy.

Neurosteroids are synthesized from steroid hormone precursors in the brain and act as positive allosteric modulators of inhibitory $GABA_A$ receptors [45,46]. Composed of various protein subunits (α1–6, β1–4, γ1–3, δ, ε, θ, ρ1–3), these receptors form heteropentameric chloride ionophore channels and produce the majority of inhibitory neurotransmission in the brain [47,48]. When activated, $GABA_A$ receptors induce an increased chloride influx into the cell, producing a hyperpolarization of the neuron that counteracts neuronal hyperexcitability and seizures [47].

$GABA_A$ receptors are divided into synaptic and extrasynaptic receptors based on location. Synaptic receptors exist within the synapse and are pervasive throughout the brain, producing phasic currents in response to the release of GABA from pre-formed vesicles [49]. In contrast, extrasynaptic $GABA_A$ receptors are found beyond the synaptic cleft and are expressed in specific regions of the brain (hippocampus, thalamus, amygdala, cerebellum). Due to constant concentrations of GABA outside of the synapse, $GABA_A$ receptors create non-desensitizing tonic currents that are regulated by stable levels of extracellular GABA [49].

Neurosteroids are powerful modulators of synaptic and extrasynaptic $GABA_A$ receptors. The mechanisms by which neurosteroids act varies. At low concentrations, neurosteroids allosterically potentiate $GABA_A$ receptors; at high concentrations, they can directly activate $GABA_A$ receptors [49,50]. Unlike benzodiazepines and barbiturates, neurosteroids increase both the frequency and duration of chloride channel opening when acting at $GABA_A$ receptors [51]. While the exact neurosteroid binding site remains undetermined, neurosteroids are believed to bind and interact with discrete sites on the receptor-channel complex located within the transmembrane domains of the α- and β-subunits [49]. Although neurosteroids act on all $GABA_A$ receptor isoforms, they impose substantial effects on extrasynaptic isoforms which contain δ-subunits, enabling neurosteroids to inhibit neuronal excitability to a greater extent by potentiating tonic inhibition [49,50].

3.2. Steroid hormones

Steroid hormones are synthesized and secreted from ovarian, gonadal and adrenal sources and play a key role in the neuroendocrine control of neuronal excitability and seizure susceptibility [40] (Table 2). In men, the main circulating steroids are androgenic steroids (testosterone and dihydrotestosterone) and adrenal corticosteroids (cortisol and aldosterone). Deoxycorticosterone is also released from the adrenal cortex in response to stress. In women, the primary reproductive steroid hormones are estrogens and progesterone, which are released during the menstrual cycle. The early follicular phase is associated with low

levels of estrogens and progesterone. Estradiol is secreted in the second half of the follicular phase and increases to a peak at midcycle, while progesterone is elevated during the luteal phase and declines before menstruation begins.

Progesterone is an anticonvulsant hormone that has a relatively higher concentration in females. Progesterone acts as an anticonvulsant agent through three primary mechanisms: negatively impacting glutamatergic (excitatory) transmission, binding to progesterone receptors (PRs), and metabolization to the inhibitory neurosteroid AP. [42,52,53]. This occurs through sequential A-ring reductions and allows AP to act as a positive allosteric modulator of $GABA_A$ receptors [39,45,54,55]. Progesterone is also metabolized to 5α-dihydroprogesterone which is known to inhibit seizures. This occurs during progesterone's conversion to AP and contributes to the anticonvulsant effects of progesterone [56,57]. Somewhat counterintuitively, it was demonstrated that PRs take longer to exhibit their anticonvulsant effects compared to the rapid conversion of progesterone to neurosteroids, suggesting that these conversions could potentially be more relevant to developing pharmaceutical treatments for various epilepsies. This conclusion is further validated by the significantly large protective ED50 of progesterone and its precipitous loss of anticonvulsant activity in the presence of finasteride, which blocks progesterone's conversion to neurosteroids [56,58].

Estrogens can affect seizure susceptibility. In general, estrogens have proconvulsant and epileptogenic properties in animals and humans [59]. There are limited studies that support protective effects of estrogens, and it may also be anticonvulsant under some circumstances [60]. However, the effect of estrogens on seizure susceptibility is highly variable and depends on factors such as treatment duration, dosage, hormonal status, and the seizure model [61]. Early studies of estradiol administration to ovariectomized rats revealed proconvulsant effects [54]. The effect of estrogens on hippocampus seizure susceptibility is controversial [59]. While estradiol has been shown to be proconvulsant in several studies, there is also evidence which supports lack of effect or protective effect of estrogens [62–64]. The effect of circulating estrogens has been studied in female rats with epilepsy [65]. Epileptic female rats show cyclic increases in epileptiform activity that coincide with their ovarian cycle, mostly attributable to estrogens. Estradiol is well-known to exacerbate seizures in women with epilepsy [66]. An increase in the ratio of estrogen-to-progesterone levels during perimenstrual period might at least partly contribute to the development of perimenstrual catamenial epilepsy [67,68].

Like progesterone's impact on GABAergic transmission, estrogen positively impacts glutamatergic transmission and produces proconvulsant actions in the brain [69,42]. Estradiol potentiates glutamatergic synaptic transmission in both male and female rats. This occurs through a combination of increased presynaptic glutamate release probability and increased postsynaptic sensitivity to glutamate and other changes in the dendritic structure [70,71]. Seizure susceptibility in females may subsequently be partly determined by physiological ratios of estrogen and progesterone. However, because of recent studies suggesting that estrogen may also display anticonvulsant properties primarily through the neuroprotective effects of the β-estradiol subtype, the impact of progesterone on female

seizure susceptibility is much more profound [63,72,73,74]. In addition, testosterone has marked impact on seizure susceptibility by metabolism to estrogens [75].

Androgens and testosterone serve as bimodal modulators of seizure susceptibility, exhibiting both anticonvulsant and proconvulsant properties [76,77,78,79,80]. Research has shown that the metabolization of testosterone to estrogens increases seizure susceptibility in both animal and human models [66]. In contrast, testosterone can inhibit seizures through its conversion to the neurosteroid androstanediol, a positive allosteric modulator of $GABA_A$ receptors [75,81].

We recently investigated the neuroprotective effects as it pertains to sex of three neurosteroids - AP, androstanediol and ganaxolone - in the experimental status epilepticus and complex partial seizure states [82]. Results revealed emphatic sex differences in their antiseizure activity, and greater sensitivity was demonstrated in females than males. As expected from it's substantial effect on extrasynaptic $GABA_A$ receptors, AP-enhanced tonic currents in hippocampal granule cells in normal wild type animals but not in those with the extrasynaptic receptor "knocked out." This lays the groundwork for understanding how sexually dimorphic, GABAergic tonic circuits in the hippocampus possibly contribute to sex differences in seizure susceptibility and neurosteroid protection. These results could prove particularly important for designing personalized neurosteroid therapies for epileptic seizures such as complex partial seizures, catamenial epilepsy, and SE [45].

3.3. Brain development, neurogenesis and glial response

Sex-based differences exist throughout brain development, and organizational effects of steroid hormones are known to impact seizures [6]. For example, brain volumes differ between males and females at birth and remain different throughout an individual's life. Early in development, organizational effects mediated by steroid hormones cause terminal differentiation of neurons and the adoption of sex-specific circuitry patterns [83]. The window for these effects is developmentally restricted but is permanent and can form dimorphic network patterns that contribute to seizure susceptibility [84].

Neurogenesis serves as a basis for sex differences in epilepsy and differs during development in a sex-specific manner. Newborn male rats display higher rates of hippocampal neurogenesis than females, whereas newborn female rats display higher rates of neurogenesis in the amygdala [85,86]. It is therefore likely that differences in neurogenesis may influence factors that cause variations in epileptogenesis. Moreover, aberrant neurogenesis is implicated as a pathologic feature of TLE in experimental models [87,88]. Although the role of neurogenesis in epilepsy is complex, sex differences in neurogenesis during epileptogenic conditions could lead to differences in the rate or incidence of epileptic seizures.

The role of glial cells, particularly astrocytes and microglia, has become highlighted in recent research as an important factor in the pathophysiology of acquired epileptogenesis and epilepsy [89,90]. Astrocytes perform many functions; they provide biochemical support for the endothelial cells which form the blood–brain barrier, provide nutrients to nervous tissue, maintain extracellular ion balance, and influence the repair and scarring processes of

neuronal injuries. Microglia play a key role in the immune response of the CNS. They serve as the main neuroimmune cells in the brain and provide neuroinflammation when a potential threat is identified. When acting without restriction, microglia have the ability to phagocytize and kill healthy neurons [91]. Indeed, microglial-induced neuronal injury has been identified across several neurodegenerative disorders including Alzheimer's and Parkinson's diseases [92].

There is experimental evidence of differential expression of astrocytes and microglia in the brain; sex-specific differences in astrocyte levels become apparent when rats transition from prepubescence to adulthood [93,94,95]. Astrocyte organization is heavily influenced by endocrine hormones, causing male astrocytes to have a stellate morphology while female astrocytes are bipolar in shape [96]. There are sex-differences in astrocyte levels throughout the brain that include various different brain regions such as the hippocampus, amygdala, and hypothalamus [96,97]. Given the crucial role astrocytes perform in synaptic communication and neurotransmission, differences in astrocyte morphology may serve as a foundation for sex differences in epilepsy. Similar differences exist for glial cells, with the hippocampus and amygdala expressing different levels of microglia between the sexes [98]. Cultures of astrocytes and microglia from female and male rats exhibit striking sex differences in functional response and expression of inflammatory markers [99,100]. The neuroprotective inflammation and immune function of microglia may significantly affect the disease processes associated with epilepsy. Although microglia and astrocytes likely play a role in determining sex differences in epilepsy, there is limited direct evidence of their differential functional responses in animal models of epileptogenesis [6].

3.4. Chloride homeostasis

There is emerging evidence which suggests that developmental chloride homeostasis influences sex differences in seizure susceptibility and drug effects in epilepsy [36] (Fig.2). The immature brain has relatively higher concentrations of intracellular chloride ions [101]. The expression of two separate Na-KCl cotransporters (NKCC1 and KCC2) is responsible for this distinction, with the neonatal brain having increased expression of NKCC1 proteins. These proteins will eventually be converted to KCC2 cotransporters on neuronal membranes as the brain matures [36]. Chloride concentrations are therefore partly determined by ratios of NKCC1 and KCC2, as NKCC1 brings chloride ions into the cell and KCC2 extrudes them [36]. When GABA binds to its receptor in neonates, chloride ions flow out of the neuron at a higher rate, which causes neuronal depolarization. This explains why neonatal seizures are not sensitive to GABAergic drugs [101]. As the brain reaches maturity, there is a gradual shift in the predominance of NKCC1 to KCC2 on the cellular membrane (Fig.2). This change results in reduced concentrations of intracellular chloride ions. When GABA binds to its receptor in this instance, chloride ions will flow down their concentration gradient and into the neuron. This will cause neuronal hyperpolarization, resulting in electrical inhibition [36]. Experimental evidence shows that NKCC1 conversion to KCC2 differs in a sex-dependent manner [102]. Females are known to experience this conversion at a higher rate, and this difference may serve as a basis for greater seizure susceptibility in male individuals [102]. Differences in levels of endogenous steroid hormones may further promote variable seizure susceptibility, as these hormones have been shown to affect KCC2

expression in a sex-specific fashion [103,104]. Changes such as these likely contribute to variation in GABAergic inhibition, but the impact of sex-dependent neonatal mechanisms on adult individuals remains under investigation.

3.5. Neurotrophic factors

A variety of neurotrophic factors and inflammatory cascades are known to influence brain injury, repair, and seizure susceptibility. Brain-derived neurotrophic factor (BDNF) and its tropomyosin-related kinase B (TrkB) receptor may promote normal neuron functioning and epileptogenesis [23,105]. However, their roles in sex differences in epilepsy remain under investigation. There is great interest in BDNF and TrkB in the field of epileptogenesis, as there appears to be some noticeable sex differences in BDNF actions. In fact, the presence and pattern of sex differences in BDNF content across brain areas exhibits prominent species differences. Female rats exhibit greater BDNF in the hippocampus, cortex, and amygdala, which are associated with epileptic pathology [106,107]. The levels of BDNF in the hippocampus is higher in males, especially in the mossy fiber pathway [108]. Male mice have higher hippocampal BDNF than females, but a greater level of BDNF is noticed in the prefrontal cortex in women [109,110]. Indeed, BDNF expression is modulated by steroid hormones estradiol, progesterone, and testosterone [105]. BDNF elicits its biological effects through activation of TrkB receptors in the brain. Heterozygous BDNF knockout mice exhibit a sex difference in the TrkB receptor pathway, with greater TrkB phosphorylation, and thus increased activation of downstream signaling, in the frontal cortex and striatum of males compared with females [111]. Sex differences in acquired epileptogenesis, caused by brain injury, are associated with differences in BDNF content [112]. Overall, BDNF levels and its signal transduction may exhibit sex differences in neuronal excitability relevant to seizure susceptibility.

4. Neurobiological mechanisms in catamenial epilepsy

Catamenial epilepsy (CE) refers to cyclical series of seizure exacerbations near specific phases of the menstrual cycle in women who are already diagnosed with epilepsy [21,113,114]. CE is quite prevalent among epileptic women, affecting between 25–70% of those in reproductive age, with the large range attributed to differences in both definition and diagnostic criteria of CE [66,115]. The occurrence of epileptic seizures during particular phases of the menstrual cycle is caused by the cyclic fluctuations of hormones, and as a result, corresponding neurosteroid levels [21,116]. When the levels of inhibitory neurosteroids drop due to a lack of their steroid hormone precursor, preexisting epilepsies may manifest themselves due to an imbalance of neuronal inhibition [117]. While there is no stringent definition as to the particular types of epilepsies and seizures that are susceptible to catamenial exacerbations, studies suggest that seizures in both partial and primary generalized epilepsies can exhibit catamenial exacerbations [21]. There are currently no FDA-approved drug therapies for treating CE, so in many cases, women diagnosed with CE are prescribed common antiepileptic drugs (AEDs) [118]. However, many women still experience catamenial exacerbations despite drug treatment.

There are three types of catamenial seizures: perimenstrual (C1, most common clinical type), periovulatory (C2), and inadequate luteal phase (C3) [66,68]. Clinical diagnosis of CE is made by longitudinally assessing menstruation and seizure records. If the first day of menstrual bleeding is considered the first day of the cycle, the menstrual cycle can be divided into four phases: (a) menstrual phase, days −3 to +3; (b) follicular phase, days +4 to +9; (c) ovulatory phase, days +10 to +16; and (d) luteal phase, days +17 to −4. After counting the number of seizures in each of the 4 phases for at least two weeks, CE is diagnosed if there is a two-fold or greater increase in frequency of seizures during a particular phase of the cycle [40]. Ovulation is not required to diagnose CE, as one study found that 16.5% of subjects experienced anovulatory cycles and associated inadequate luteal-phase seizures [119].

4.1 Neuroendocrine mechanisms

The neuroendocrine explanation for CE may be understood by general aspects of the interplay between hormones and seizures. As previously discussed, the delicate balance between the normally proconvulsant molecule estradiol (and as a result, the hormone estrogen) and the anticonvulsant hormone progesterone underlies the changes in seizure susceptibility associated with CE. Estradiol levels rise during both the follicular and luteal phase of the menstrual cycle, subsequently increasing the estrogen:progesterone ratio and possibly an epileptic woman's likelihood of displaying perimenstrual seizures [67,115,120]. The waxing and waning of progesterone levels in the menstrual cycle produce corresponding increases and decreases in seizure susceptibility, respectively [66]. Two examples are the mid-luteal and pre-menstrual phases. Seizure frequency decreases at high progesterone levels during the mid-luteal phase and increases before menstruation when progesterone levels are significantly lower [121]. Recent studies suggest that perimenstrual catamenial seizures are tightly correlated with the swift fall in progesterone near menstruation [122].

Among the variety of neurosteroids present in the brain, research indicates that AP (brexanolone), tetrahydrodeoxycorticosterone (THDOC), and androstanediol provide the most neuroprotection against epileptic seizures [81,123]. During their synthesis from steroid hormone precursors, the 5α-reduction of the A-ring converts intermediates into neuroactive steroids [124]. Much of the increase in seizure susceptibility during the phases of the menstrual cycle that feature low levels of progesterone are attributed to the loss of corresponding neurosteroids and their anticonvulsant effects [66,74,116,117,125]. An intriguing phenomenon occurs during the perimenstrual period regarding the relative abundance of extrasynaptic $GABA_A$ receptors. During this period, extrasynaptic $GABA_A$ receptors are notably upregulated above normal, with possible molecular mechanisms underlying this phenomenon discussed in the next section [126]. This overexpression of extrasynaptic GAB_A receptors provides neurosteroids with an abundance of locations to exert their anticonvulsant effects, particularly as it relates to perimenstrual seizures in CE [50].

4.2 Experimental models

There are several features of an ideal CE model [127,128,129]. It should reflect pathophysiology similar to those of catamenial seizures in women with epilepsy, exhibit

appropriate menstrual seizure phenotypes, be consistent with the neuroendocrine fluctuations of women with epilepsy, exhibit appropriate latency following steroid hormone fluctuations or withdrawal period, and respond to drug therapy with resistance to certain anticonvulsants. Because CE is so diverse in its causes and manifestations, no lone animal model can fully epitomize the gamut of human catamenial seizure phenotypes. Thus, screening novel therapeutics and investigating pathological mechanisms in a wide range of animal models is of utmost importance.

We developed both rat and mouse models, utilizing healthy and epileptic rats and mice, on the premise of creating a hormonal milieu of the perimenstrual period [129]. This was done by creating a variety of manipulations through the use of pseudopregnancies, the exogenous administration of progesterone, and the utilization of a spontaneous seizure model. Both mice and rats were subjected to studies that mimicked the surge and precipitous drop of progesterone and corresponding neurosteroids during the perimenstrual period [69,130]. These studies produced a neurosteroid withdrawal period analogous to common catamenial seizure occurrences. It was found that during this time the seizure threshold dropped significantly before returning to baseline within 72 hours. During these periods a number of therapeutic agents were tested, but neuroactive steroids proved to offer the best protective ability [130]. Furthermore, we tested the readily bioavailable synthetic neurosteroid ganaxolone (AP analog), which shifted the dose response to the left, suggesting that animals in the withdrawal phase are more sensitive to neurosteroids [131].

We recently replicated the above paradigms in two distinct mouse models to allow for more mechanistic studies [57,132]. These studies revolve around the notion that seizure susceptibility and neurosteroid levels are inversely related in females in association with specific changes in $GABA_A$ receptor subunit plasticity. First, a female hippocampal kindling model was created to mimic the chronic seizure condition. Second, these mice were administered varying levels of neurosteroids, similar to what is seen in the ovarian cycle. Finally, we adopted two separate pharmacological methods of inducing increased levels of neurosteroids: (a) chronic exogenous progesterone treatment, and (b) a gonadotropin administration to induce endogenous neurosteroid synthesis. The gonadotropin-induced neurosteroid synthesis and withdrawal paradigm appears more physiologically relevant than the exogenous progesterone treatment, as the withdrawal paradigm is induced by the neurosteroid synthesis inhibitor finasteride [132]. We have found that the mouse model of perimenstrual CE is useful for the investigation of disease mechanisms and exploring the efficacy of new therapeutic techniques. However, there are some limitations with these preclinical models stemming from differences in human vs. rodent menstrual cycles. In rodents the estrous cycle duration is 4–7 days, whereas in women it lasts roughly 28 days.

4.3 Neurosteroid replacement therapy

Since there are currently no FDA-approved therapies specifically for catamenial seizures, particularly those in the perimenstrual period, the neurosteroid withdrawal model has and is being used as a basis for developing new therapies for CE [51,133]. Consistent with the observation that women with catamenial epilepsy do not respond to common AEDs, a key result from this model is that conventional AEDs have a reduced potency in protecting

against catamenial seizures, producing a form of a pharmacoresistant paradigm. However, we found that neurosteroids and their synthetic analogs have enhanced activity in the perimenstrual CE model [131,133,134]. This led to the idea that “neurosteroid replacement” may be an effective method for countering catamenial seizure exacerbations [135]. We hypothesized that a neurosteroid or synthetic analog could be administered throughout the month, at a low dose to avoid sedative side effects and produce little anticonvulsant activity during most of the menstrual cycle, to serve as a CE therapeutic.

While the molecular mechanisms underlying the enhanced neurosteroid sensitivity in catamenial epilepsy remain unclear, a delta-force hypothesis has been coined to explain this phenomenon [41,136]. We recently discovered that the extrasynaptic $GABA_A$ receptors in the dentate gyrus of a mouse perimenstrual model of CE appear to be plastic [126,137]. In summary, it is posited that the drop in neurosteroids during the perimenstrual period catalyzes a selective overexpression of α4δ subunits of $GABA_A$ receptors in the dentate gyrus granule cells. This alone is not adequate to abate the increased seizure susceptibility due to the absence of AP, but this pathologic rise in α4δ subunits could possibly act as a vehicle catalyst (“Trojan Horse”) for exogenously administered AP to prevent seizures. This unique sensitivity to AP displayed by women with perimenstrual CE is concordant with the results of the NIH progesterone trial, where the responder group was in fact women with perimenstrual CE [138]. This group demonstrated a significant post-treatment surge in AP, an outcome that suggests perimenstrual CE would be an ideal candidate for testing the therapeutic benefits of a brief, repetitive neurosteroid administration during the perimenstrual period [138]. Taken together, this molecular mechanism represents a molecular rationale for neurosteroid replacement therapy.

5. Conclusions and future directions

Sex differences are evident in many epilepsies and seizure conditions. The current evidence suggests that men exhibit greater overall seizure susceptibility than women, while women exhibit greater fluctuations in seizure susceptibility, such as menstrual cycle-related catamenial seizures. However, the precise changes in neuroendocrine factors and molecular mechanisms remain poorly understood. Steroid hormones and endogenous inhibitory neurosteroids are important in gender differences as it relates to susceptibility to epileptic seizures. Neurosteroids may exert sex differences in their protection against neuronal excitability and seizures. It is likely that differences in steroid hormones or neurosteroid levels in the brain in males and female may contribute to sex differences in seizure control and epileptic seizures. Besides factors like brain development, chloride homeostasis, neurotrophic factors and neurogenesis, sexual dimorphism in specific receptors and function may account for the sex differences in seizure susceptibility and resistance. It is likely that endogenous neurosteroids may mediate sex differences in seizure susceptibility. Consequently, neurosteroids exhibit greater antiseizure potency in females than males, likely due to greater abundance of extrasynaptic $GABA_A$ receptors and also differences in neural circuits that regulate seizure susceptibility. Catamenial epilepsy, which is attributed to withdrawal or loss of endogenous neurosteroids around the perimenstrual period, is a unique gender-specific epilepsy in women. Neurosteroid replacement therapy is a viable approach to effectively control catamenial seizures in women with epilepsy. Additional research is

warranted to identify the structural and neuroendocrine map of sex differences in the epilepsies.

Acknowledgements

This work was supported by NIH grants NS052158 and NS051398 (to DSR). Dr. Reddy's research work was supported by the CounterACT Program, National Institutes of Health, Office of the Director and the National Institute of Neurologic Disorders and Stroke [Grant U01-NS083460, U01-NS117209 and U01-NS117278].

ABBREVIATIONS:

AED	antiepileptic drug
AP	allopregnanolone (brexanolone)
BDNF	brain derived neurotrophic factor
GX	ganaxolone
NKCC1	Na-K-Cl cotransporter
PCDH19	Protocadherin 19
THDOC	tetrahydrodeoxycorticosterone
TLE	temporal lobe epilepsy
TrkB	tropomyosin-related kinase B

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Highlights

- Sex differences exist in epilepsy and epileptogenesis, but mechanisms remain unclear.
- Sex-related differences in morphology and circuits in men and women may explain differential vulnerability to seizures and epileptogenic injuries.
- Changes in seizure sensitivity are due to neurosteroids as well as receptor signaling systems.
- Potential neural basis for sex differences in epilepsies include differences in neurogenesis, chloride homeostasis, and neurotrophic and glial responses.
- A greater understanding of sex differences is needed for designing effective therapies for epilepsy and disease-modification of epileptogenesis.

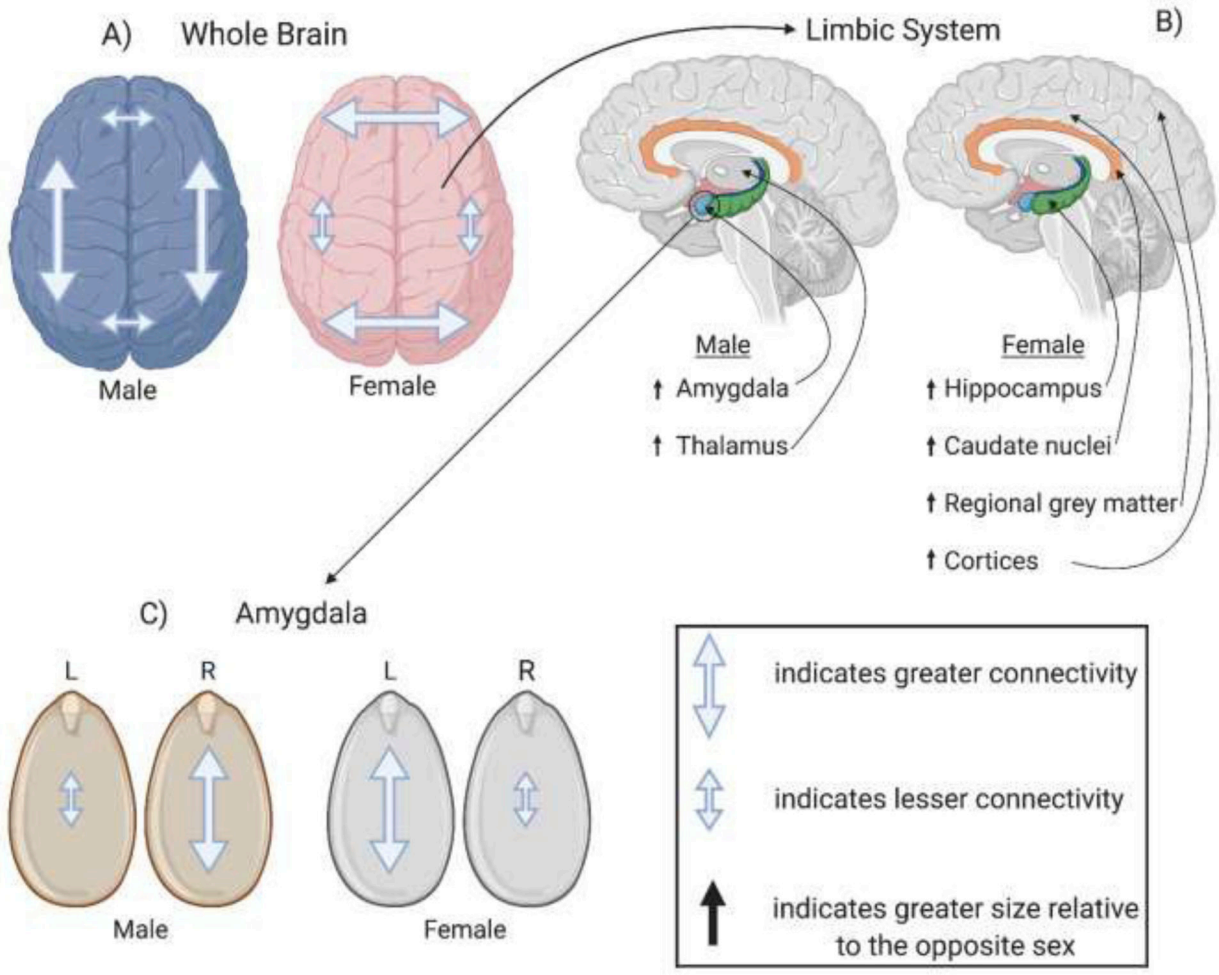

Fig. 1.

Sexual dimorphism within the brain. A) Males exhibit greater intrahemispheric connectivity, whereas females exhibit greater interhemispheric connectivity. B) Within the limbic system, males feature larger amygdalae and thalami, and females feature larger hippocampi, caudate nuclei, regional grey matter, and cortices. C) Males exhibit greater connectivity within the right amygdala than the left, whereas females exhibit greater connectivity in the left amygdala.

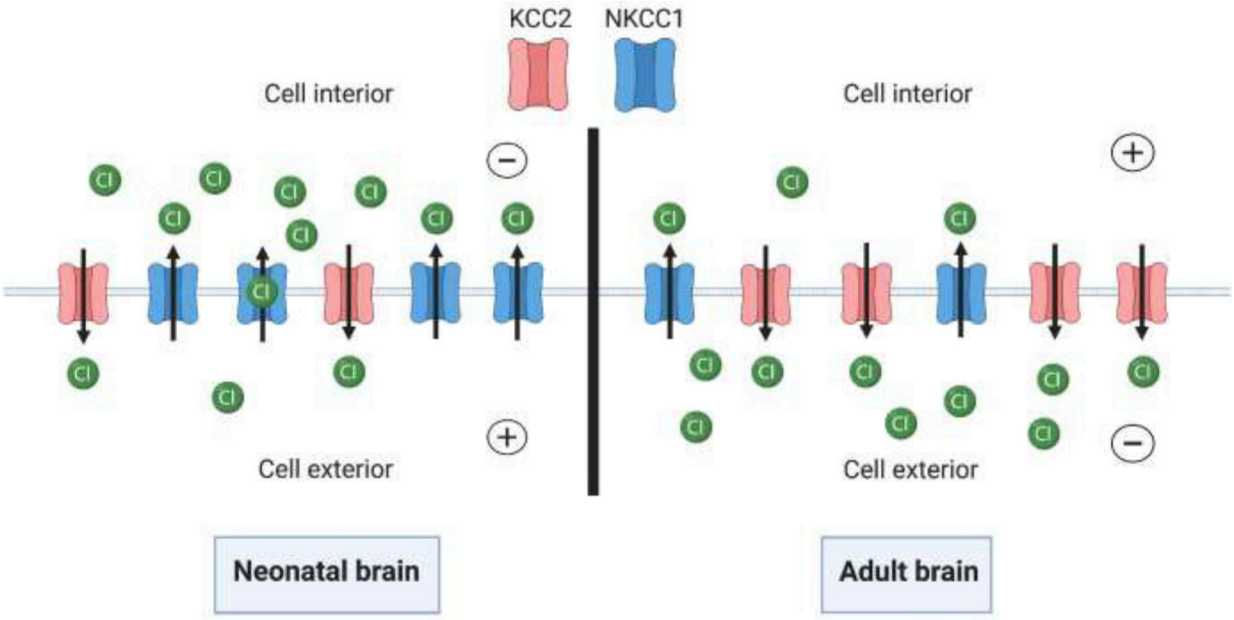

Fig. 2.

Age-dependent neuronal chloride homeostasis. The image depicts the relative abundance of NKCC1/KCC2 chloride cotransporters in neonatal/adult brains. As the brain matures, NKCC1 transport proteins convert to KCC2 proteins, reversing chloride concentrations on either side of the neuronal membrane. This figure was created using BioRender.com.

Table 1.

A breakdown of the sex-related incidence preferences of several common epilepsy syndromes.

Epilepsy Syndrome	Male or Female Preponderance	Citation
Idiopathic generalized epilepsy	Female	[8,9]
Cryptogenic localization-related epilepsy	Female	[10]
PCDH19-related epilepsy	Female	[18]
Childhood absence epilepsy	Female	[19]
Photosensitive epilepsy	Female	[20]
Catamenial epilepsy	Only female	[21]
Localization-related symptomatic epilepsy	Male	[11]
Injury-induced epilepsy	Male	[10]
Status epilepticus	Male	[22]
Focal cortical dysplasia	Male	[23]
Perinodular heterotopia	Male	[23]
Epilepsy as a whole	Male	[12]

Table 2.

List of endogenous steroids and neurosteroids that modulate seizure susceptibility.

Anticonvulsant steroids	**Proconvulsant steroids**
Progesterone	Estradiol
Allopregnanolone	Pregnenolone sulfate
Pregnanolone	Dehydroepiandrosterone sulfate
Dihydroprogesterone	Cortisol
Androstanediol	11-Deoxycortisol
Etiocholanone	
Dihydrotestosterone	
Deoxycorticosterone	
Dihydrodeoxycorticosterone	
Allotetrahydrodeoxycorticosterone	