Hormones and Epilepsy

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Summary

Hormones are crucial systemic players and act at different sites of the entire body including the brain. The brain is not only the target of hormone action, but also serves as the "conductor" of the "neuro-endocrine symphony". Changes in neuronal activity, such as seizures in epileptic patients, may affect hormonal regulation and secretion. In turn, hormones modify susceptibility to develop seizures. Epilepsy itself may directly influence the endocrine control centres, the hypothalamic-pituitary axis, thus altering the release of gonadotropin releasing hormone and therefore affect gonadal hormone concentrations resulting in changed sexual function. Awareness of how hormones relieve or exacerbate seizure frequency and severity, as well as of *how* seizures and epilepsy may significantly affect reproductive and sexual function by interacting with hormone secretion and metabolism is important. In addition, not only changes in neuronal activity may affect hormone secretion and metabolism in patients with epilepsy, but also antiepileptic drugs may have deleterious effects.

In summary, epilepsy, antiepileptic drugs and hormones display complex interactions. Hormones may alter seizure threshold, change the frequency and severity of seizures. In turn, epilepsy and/or antiepileptic drugs can compromise the reproductive hormonal and sexual functions in women and man. A better understanding of hormone – brain interactions should promote a variety of innovative approaches to an improved treatment of epilepsy through both behavioural and pharmaceutical interventions.

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Key words: Epilepsy, gonadal hormones, neuronal activity, interaction, stress

Hormone und Epilepsie

Hormone sind essenzielle systemische Steuermoleküle, die an verschiedensten Orten im gesamten Körper, insbesondere auch im Gehirn ihre Wirkung entfalten. Dabei ist das Gehirn nicht nur Wirkort der Hormone, sondern es dient auch gewissermassen als "Dirigent" der "neuroendokrinen Symphonie". Veränderungen in der neuronalen Aktivität, wie dies bei epileptischen Anfällen der Fall ist, können die Regulation und Freisetzung der Hormone beeinflussen. Umgekehrt verändern Hormone die Anfälligkeit, epileptische Anfälle zu erleiden. Die Epilepsie selber kann einen Einfluss auf die endokrinen Kontrollzentren, die hypothalamisch-hypophysäre Achse, ausüben und folglich die Sekretion von gonadotropem „Releasing"-Hormon verändern, was die Konzentration der Sexualhormone beeinflusst und letztlich in eine geänderte sexuelle Funktion mündet. Es ist auch wichtig, sich bewusst werden zu lassen, wie Hormone epileptische Anfälle in Frequenz und Stärke vermindern oder verstärken können, genauso wie es von Bedeutung ist, wie epileptische Anfälle und Epilepsie die sexuellen und reproduktiven Funktionen durch Interaktionen mit der Hormonsekretion und ihrem Metabolismus beeinflussen können. Zusätzlich können nicht nur Änderungen in der neuronalen Erregbarkeit einen Einfluss auf die Hormonsekretion und den -metabolismus ausüben, sondern auch Antiepileptika können entscheidende, oftmals ungünstige Effekte ausüben.

Zusammengefasst stehen Epilepsie, Antiepileptika und Hormone in einem gegenseitigen komplexen Wechselspiel von Abhängigkeiten. Hormone können die Krampfschwelle, die Häufigkeit und den Schweregrad von epileptischen Anfällen beeinflussen. Andererseits können die Epilepsie und antiepileptische Medikamente die reproduktiven hormonellen und sexuellen Funktionen bei Männern und Frauen beeinträchtigen. Ein besseres Verständnis der Wechselwirkung zwischen Hormonen und dem Gehirn dürfte eine Vielfalt von Möglichkeiten für neue, innovative, pharmakologische und verhaltensmässige Behandlungsstrategien bei Patientinnen und Patienten mit Epilepsie eröffnen.

Schlüsselwörter: Epilepsie, Sexualhormone, neuronale Aktivität, Interaktion, Stress

Hormones et épilepsie

Les hormones sont des molécules de commande systémique essentielles qui déploient leurs effets en différents endroits de tout le corps, en particulier dans le cerveau. Mais le cerveau n'est pas seulement un siège d'action des hormones, il est en quelque sorte le « chef d'orchestre » qui dirige la « symphonie neuroendocrinienne ». Les modifications de l'activité neuronale telles qu'on les observe lors d'une crise épileptique peuvent influencer la régulation et la libération

des hormones. A l'inverse, les hormones peuvent aussi modifier la sensibilité aux crises épileptiques. Quant à l'épilepsie elle-même, elle peut avoir une influence sur les centres de contrôle endocriniens de l'axe hypothalamo-hypophysaire et de ce fait modifier la sécrétion de l'hormone de libération gonadotrope, ce qui a une incidence sur la concentration des hormones sexuelles et débouche en fin de compte sur une fonction sexuelle modifiée. Il est aussi important de comprendre comment les hormones peuvent atténuer ou intensifier les crises épileptiques tant en termes de fréquence que d'intensité, tout comme il est important de savoir comment les crises épileptiques et l'épilepsie peuvent influencer les fonctions sexuelles et reproductives par interaction avec la sécrétion d'hormones et leur métabolisme. A cela s'ajoute que la sécrétion et le métabolisme hormonal peuvent être influencés non seulement par des modifications de l'excitabilité neuronale, mais aussi par les antiépileptiques dont les effets peuvent être déterminants et souvent néfastes.

En résumé, l'épilepsie, les antiépileptiques et les hormones forment une constellation complexe d'interactions et d'interdépendances changeantes. Les hormones peuvent influencer le seuil de crampe, la fréquence et la gravité de crises épileptiques. A l'opposé, l'épilepsie et les médicaments antiépileptiques peuvent influencer les fonctions reproductives hormonales et sexuelles de l'homme et de la femme. Une meilleure compréhension des interactions entre hormones et cerveau promet de révéler une multitude de pistes et de stratégies novatrices dans le traitement pharmacologique et comportemental des patientes et des patients épileptiques.

Mots clés :épilepsie, hormones sexuelles, activité neuronale, interaction, stress

Introduction

Hormones are crucial systemic players and act at different sites of the entire body including the brain. The brain is not only the target of hormone action but also acts as "conductor" of the "neuro-endocrine symphony". The endocrine and the nervous system both are systemic players which mutually interact at different levels.

Several studies performed during the last century have clearly illustrated the role of the brain as part of the endocrine system [1]. The pioneering work of Ernst and Bertha Scharrer demonstrated the presence of the so-called neurosecretory neurons in the hypothalamus of all vertebrates [2]. They discovered the pivotal neuroendocrine axis including the following structures: the hypothalamus, the pituitary and the "peripheral" glands. An important group of hormones which derive from the hypothalamus were called "releasing hormones" (e.g. gonadotropin releasing hormone (GnRH), corticotropin releasing hormone (CRH), thyrotropin releasing hormone (TRH)) which when secreted stimulate the release of pituitary hormones (e.g. follicle stimulating hormone, prolactin, luteinizing hormone, adrenocorticotropic hormone, thyreotropin) which in turn stimulate the hormone production in peripheral glands (e.g. estrogens, testosterone, progesterone, thyroxin). At different levels, these hormones are controlled by complex feedback regulations to ensure homeostasis.

There is abundancy of neuroactive hormones which contribute to the "neuro-endocrine symphony"; however, this article will focus only on gonadal hormones, specifically estrogen, testosterone and progesterone and their effect on the brain and specifically on neuronal excitability.

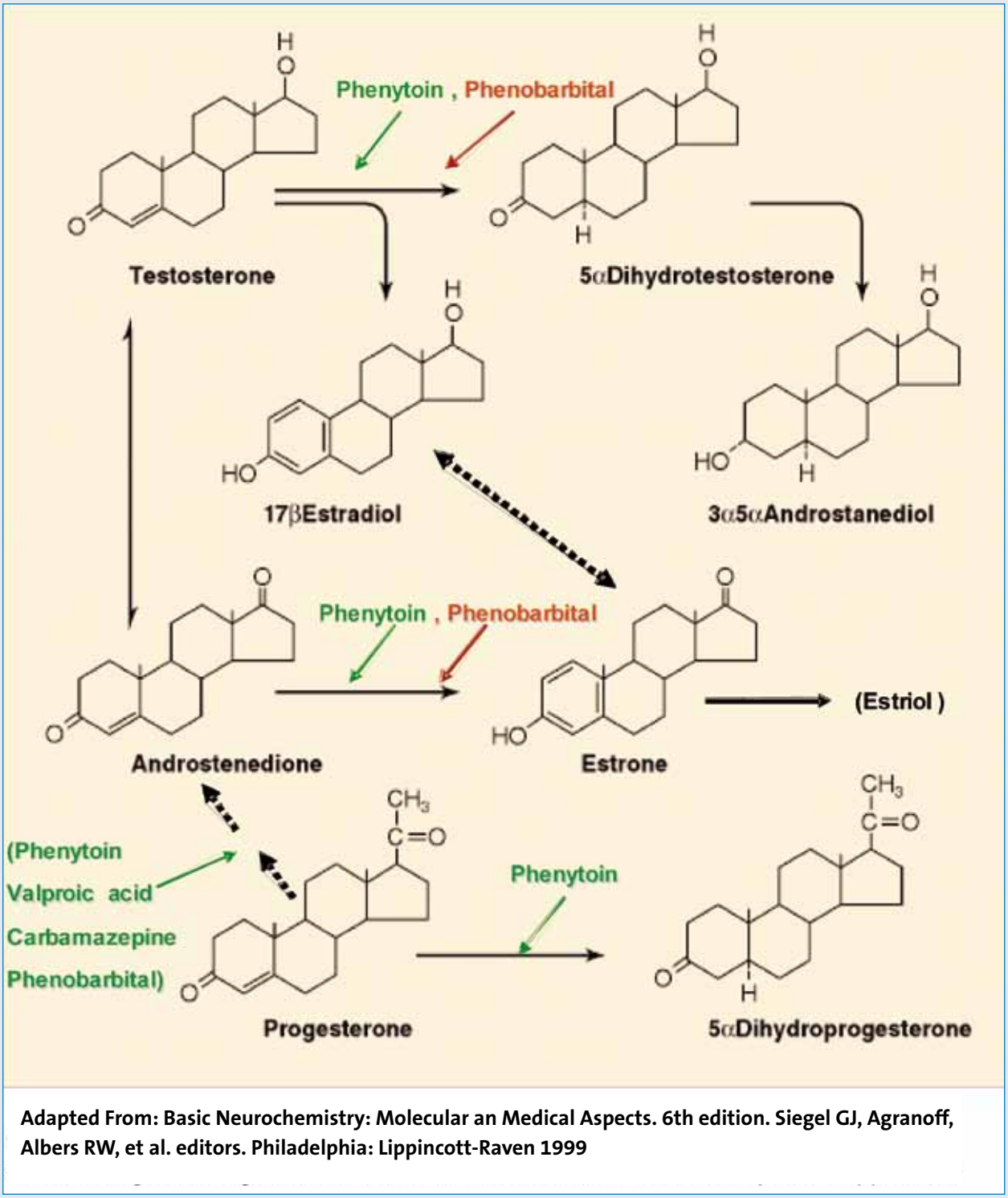
Gonadal hormones and the brain

General considerations

Gonadal hormones are produced mainly in the ovaries or testes, but they all can also be synthesized in the brain. They belong to the family of steroid hormones together with glucocorticoids and dehydroepiandrosterone which are essentially produced in the adrenal gland [3, 4].The effects of steroid hormones are mediated by slow genomic (classic pathway), as well as rapid non-genomic mechanisms; therefore they act on both nuclear AND membrane receptors [5].The advent of antibodies directed against steroid receptors and steroid receptor cloning now allows for the measurement of intracellular steroid receptors themselves or their mRNAs by immunocytochemistry and in situ hybridization histochemistry [4]. Several studies investigated the presence and distribution of steroid hormone receptors within the central nervous system. Surprisingly, they found steroid receptors in variable quantities according to location and age not only in the hypothalamus or the pituitary gland, but also in several other brain regions, such as the amygdala, the hippocampus, the cerebral cortex, the midbrain, the cerebellum, the medulla, or the spinal cord [6-10].

Estrogens

Estrogens are generated from cholesterol via testosterone in the ovaries, but also by the brain and by body fat deposits in both males and females [11]. There are several sources of estrogen formation in fat tissue and brain **(Figure 1**). The three principal circulating estrogens are estrone (E1), estradiol (E2), and estriol (E3); they all can bind at estrogen receptors, however their mode of action may differ. Estrogens act through two principal nuclear receptors, the estrogen-α and -β receptors (ER-α and ER-β) which are differentially



Adapted From: Basic Neurochemistry: Molecular an Medical Aspects. 6th edition. Siegel GJ, Agranoff, Albers RW, et al. editors. Philadelphia: Lippincott-Raven 1999

Figure 1: Important metabolic transformations of steroids that may also be carried out by neural tissue and the influence of anticonvulsant drugs .

expressed in the brain. Recently, the concept of membrane receptors has evolved and the nature of these types of receptors is currently under study. ER-α is highly expressed in the pituitary, hypothalamus, hypothalamic preoptic area, and amygdale, while ER-β is highly prevalent within the hypothalamic preoptic area, ventromedial nucleus of the hypothalamus, paraventricular nucleus, dorsal raphe, substantia nigra, and pontine nuclei of the midbrain. Thus, estrogen is not only acting on the hypothalamus affecting ovulation and reproductive behaviour, but it also exerts many effects on brain areas that are important, for example, for learning, memory, emotions, as well as motor coordination and pain sensitivity [12]. These estrogen-targeted actions

are provided by many widely projecting neural systems such as the basal forebrain cholinergic system, the midbrain serotonin and dopamine systems and the brainstem cholinergic and noradrenergic systems (**Figure 2**).

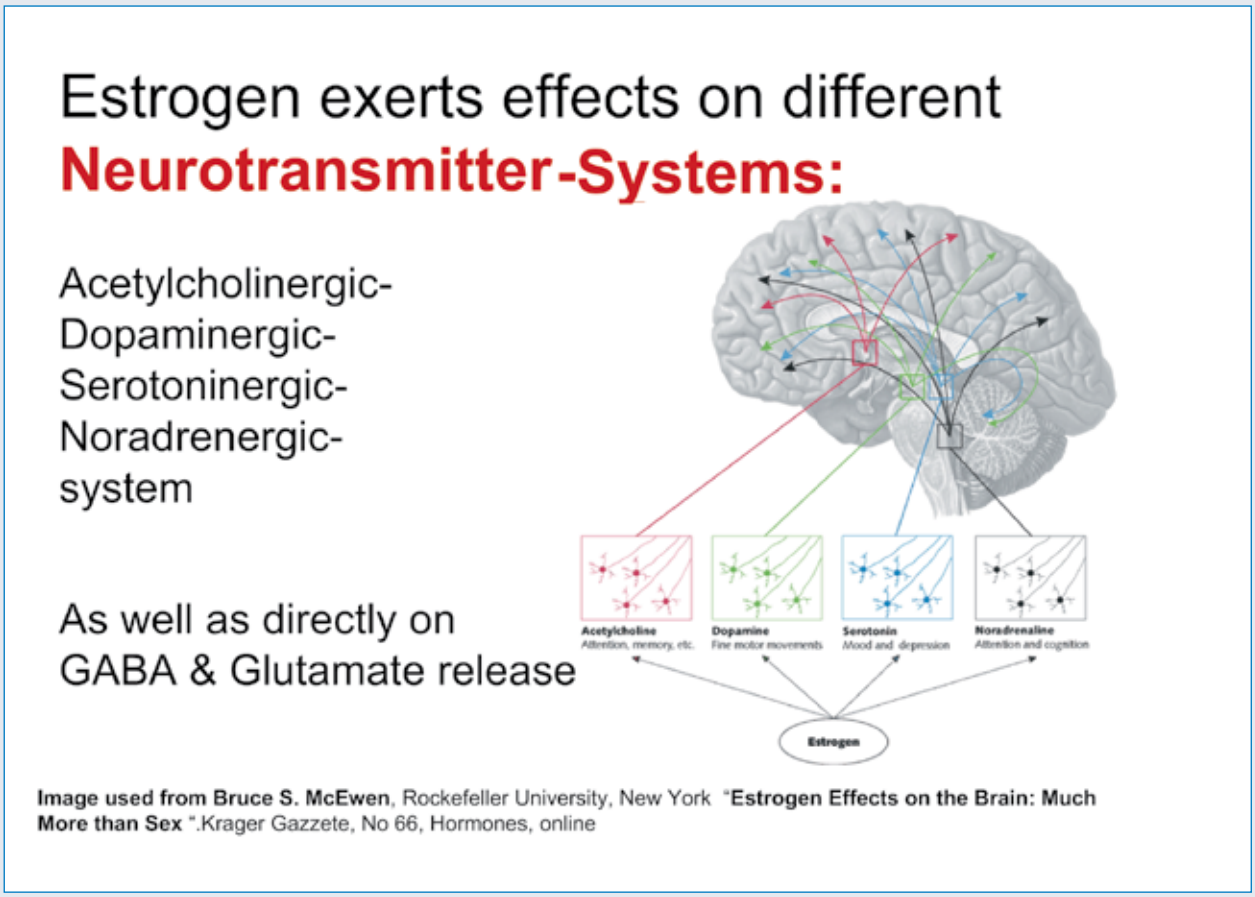


Figure 2: Several neurotransmitter systems which project widely into the forebrain are influenced by circulating estrogens.

In addition it is known that estrogens have antioxidative effects within the brain [13, 14], promote vasodilatation and consecutive increased cerebral blood flow [15], regulate plasticity of axonal terminals, dendritic branches, spines and receptors [16-21], lead to increased mitochondrial energy production [22-24] and may reduce neuronal cell apoptosis [25]. On one hand, estrogen effects may result in an increase of neuronal excitability, on the other hand, estrogens also might protect neurons against this same glutamate excitotoxicity by reducing neuronal cell death after the firing [4, 26-28] .

It is believed that estradiol may exert direct excitatory effects at the neuronal membrane, where it augments N-methyl-D-aspartate-(NMDA-)mediated glutamate receptor activity. This enhances the resting discharge rates of neurons in a number of brain areas including the hippocampus, where estradiol increases exitability of the hippocampal CA1 pyramidal neurons and induces repetitive firing. In addition, it may potentiate neuronal excitability by regulating neuronal plasticity and it may modulate neurotransmitters which leads also to neuronal excitability summarized from [29]). The above discussed mechanisms explain only some pathways of several in the literature, which are related to the effects of estrogen. The role of estrogens on neuronal excitability, however, is very complex and it is unlikely that estrogen would exert single, uniform actions given our understanding of its complex pharmacological and physiological relationships. The modulatory effects are likely to depend on endocrine state, relative concentration to other hormones such as progesterone, metabolism, brain region, individual threshold and many other factors [4]. For example, prior to ovulation, the rise in estrogen is followed within a few hours by an increase in progesterone levels, which – at that point in the cycle – appears to potentiate many of the neuroendocrine effects of estrogen [30, 31]. However, progesterone also antagonizes the effects of estrogen at other periods of the menstrual cycle, when progesterone is elevated while estrogen is not [32, 33].

Estrogens can clearly increase excitability; however, there are other aspects to consider: Estradiol has been shown to increase the levels of glutamic acid decarboxylase (GAD), the rate-limiting synthetic enzyme for γ-aminobutyric acid (GABA), and thus may increase

levels of GABA [34, 35]. It can also induce neuropeptide Y (NPY) which has actions generally consistent with an anticonvulsant effect [36], just to mention two of them. Thus, estrogens may exert very different and even opposite effects depending on a variety of factors.

Progesterone

Progesterone, and its immediate 5α-reduced metabolite dihydroprogesterone, are two natural progestins that bind to nuclear progesterone receptors [4]. Dihydroprogesterone is further metabolized to a neuroactive steroid, allopregnanolone which is a potent modulator of GABA-A-receptor function [37]. Thus, theoretically, administration of progesterone, dihydroprogesterone, or allopregnanolone may lead to effects mediated by either progesterone receptor activation or agonist-like actions at GABA-A-receptors as well as antagonist-like actions at glutamate receptors [38]. This may result in an increase in inhibitory and a decrease in excitatory tone in the brain, respectively. There are two forms of progesterone receptors (PRs), PR-A and PR-B. They are identical to one another except for an additional 164 amino acids at the N-terminus of PR-B [4]. Remarkably, PRs are broadly expressed throughout the brain and can be detected in every neural cell type [26]. Progesterone receptors are often co-localized with estrogen receptors and estrogen may be necessary for expression of the progesterone receptors in certain areas of the brain [39]. Progesterone can act antagonistically, synergistically, or independently of the effects of estrogen [40-45]. When assessing the effects of progesterone on excitability it is important to note that the mode of action and effects of progesterone differ depending on its relative concentrations. Thus, progesterone sensitivity highly relies on prior or concurrent estrogen exposure, at least in part, because estrogens induce progesterone receptor synthesis in the brain, as well as in many other tissues [46, 47]. In addition, progesterone has multiple non-reproductive effects in the central nervous system: it works as an antioxidant, increases mitochondrial function, promotes neurogenesis and regeneration, as well as myelination and recovery from traumatic brain injury [26].

Testosterone

Testosterone represents the primary steroidal product of the testes, but it is also synthesized in the thecal interstitial cells of the ovary where it is converted to estradiol in the granulosa cells of the primordial follicle. The knowledge of the effects of testosterone on the brain is still limited when compared to estrogen and progesterone, especially in humans. The two androgen receptors AR-A and AR-B are present in different nuclei of the hypothalamus, but they are also widely spread over the brain, including structures such as the septum, medial preoptic area, stria terminalis, frontal cortex, amygdala and premammillary nucleus [48]. Only a few studies have examined the effect of testosterone on neurotransmitter systems [49] and it has been shown that testosterone has especially effects on the dopaminergic system which mediates for example certain aspects of male behaviour [50-52]. In addition, testosterone may exert its effects directly via activation of GABA-A- and blocking glutamate receptors, what leads to reduced neuronal excitability similar to progesterone [38]. Testosterone, in contrary to estrogen, has pro-inflammatory properties and increases vascular tone [53]. Variable effects of androgens on the brain may be due to actions of its metabolites. Testosterone is aromatized to E2 which can have neuroexcitatory effects, as well as to dihydrotestosterone (DHT) which can decrease excitatory glutamatergic activity and be converted by 3α-hydroxysteroid dehydrogenase to 5α androstane-3α,17α-diol (3α-diol), which has inhibitory effects as well [38].

In conclusion, gonadal hormones and their metabolites exert very complex, variable, and time-sensitive effects on the brain and its neuronal excitability, either directly via specific receptors or via neurotransmitters or indirectly by, for example, stimulating the release of other peptides.

Gonadal hormones and their influence on epileptic activity

Seizures are the clinical manifestation of abnormal, excessive excitation and synchronization of a population of cortical neurons. Neuronal excitability is not equal to clinical or purely electroencephalographic subclinical seizures. Different effects of hormones have been observed on the level of neuronal excitability, though the effects on seizures in epileptic patients are even more complex. Given this complexity and given the heterogenous study designs, the multifaceted and controversial relationship of gonadal hormones and seizures in patients with epilepsy may be partly explained.

Electrophysiological studies have shown that acute administration of conjugated equine estrogens on the cerebral cortex lead to epileptogenic effects [54]. Physiological doses of estradiol activated spike discharges [55] and lowered the thresholds of seizures in the maximal electroshock-, kindling-, ethyl chloride- and other models of experimental epileptogenensis in animals [56-58]. Clinically, Logothetis et al. showed that intravenously administered conjugated estrogens activated epileptiform discharges in 11 out of 16 patients and were associated with clinical seizures in four [56]. In contrary, other studies showed no effect on seizure activity or, conversely, even a decline in seizure frequency [59].

The studies examining the effects of *progesterone* on seizures point in a more uniform direction: in general, progesterone administration appears to be rather anticonvulsant. Some small clinical studies in women with seizures showed that intravenously infused progesterone or cyclic progesterone therapy suppressed interictal epileptiform discharges in the EEG and clinically improved seizure control [60-62]. However, it is not clear whether progesterone itself is responsible for these effects, or whether the effects are mediated through its metabolites, especially allopregnanolone. Interestingly, synthetic progestins, such as those used in contraceptives, do not necessarily have an anticonvulsant effect [4].

Fluctuations of the *estrogen-to-progesterone-ratio* have been suggested to be the trigger of seizure exacerbation during the menstrual cycle. Likewise, the decline in progesterone levels during menopause was associated with a decrease in seizure frequency [63]. Seizures do not occur randomly in most men and women with epilepsy [64]. They tend to cluster and these seizure clusters, in turn, may occur with temporal (circadian or menstrual) rhythmicity. For women in whom seizures cluster in relation to the menstrual cycle, the term "catamenial epilepsy" (CE) has been coined.

Catamenial Epilepsy is not uncommon; it was originally described by early Greek physicians and the term derives from "katamenios", meaning "monthly" [65]. A twofold increase in average daily frequency during the phase of exacerbation relative to other phases defines catamenial epilepsy for research purposes [66]. Herzog et al. additionally categorized catamenial epilepsy into three subgroups: C1: during the perimenstrual period (days -3 to 3)/ C2: ovulation days (10 to 13)/ C3: days 10 to 30 in *inadequate* luteal phase cycles and anovulatory cycles [66, 67] (see also **Figure 3**). Seizure frequency was associated with the serum estradiol/ progesterone-ratio in ovulatory cycles. The hypothesis behind argues that a pro-convulsive state rises if this ratio is high (either when estrogen is high compared to progesterone or progesterone is low compared to estrogen or both). This situation occurs in the 3 subgroups C1-C3 described above by Herzog et al. whereby the most common and pathophysiologically compelling is the subgroup during ovulation, C2. In addition, specifically premenstrual exacerbation of seizures may also be related to the decline in anticonvulsant medication levels [68, 69].

The best way of *establishing the diagnosis* of CE relies on a carefully documenting seizure diary in relation to the menstrual cycle of the patient, on checking midluteal serum progesterone to see whether the luteal phase is inadequate, and on measuring the AED levels on day 22 and day 1 because of a probably increased drug metabolism during this period (see **Figure 4**).

First line *treatments of hormonal related seizures in women* are AEDs (e.g. gabapentin has shown good effects in CE since it seems to affect E2-induced changes in neuronal hyperexitability [59]) as in other epileptic patients. If low AED levels are found in certain phases of the menstrual cycles it may be helpful to increase the dose slightly around that time. However, there is some evidence that certain women with clear CE may additionally benefit from endocrine treatment. Since progesterone has shown consistently rather anticonvulsive effects throughout different studies, treatment with progesterone was evaluated as an adjunctive treatment in appropriate patients. Two main approaches have been evaluated: i) the *cyclic progesterone therapy* supplementing progesterone during the luteal phase and ii) the *suppressive therapy* tempting to suppress the menstrual cycle usually by injectable progestins (i.e. synthetic progestational agents) or GnRH analogues. In one study of women with refractory partial seizures and normal ovulatory cycles a medroxyprogesterone dose large enough to induce amenorrhea (120 to 150 mg every 6 to 12 weeks intramuscularly) resulted in a 40% average seizure reduction [60]. Oral synthetic progestational agents have not shown any beneficial effects, but cyclic progesterone (i.e., a naturally occurring progestational compound) has been shown to reduce seizure frequency in two open label trials of adjunctive therapy [70, 71]. Progesterone was more efficient when administered during the entire second half of the cycle rather then just perimenstrually, and then tapered and discontinued gradually [71]. A 3- year follow-up study demonstrated that improved seizure control persisted during continued treatment [61]. However, potential side effects should not be underestimated, including depression, sedation and breakthrough vaginal bleedings. Concomitant therapy with AED should be monitored closely since in some cases progesterone treatment has been associated with changes in AED levels. There are only a few studies concerning GnRH analogue therapies creating a medical oophorectomy and there are no controlled clinical trials. Two reports have shown a benefit in women with CE. Bauer et al. treated 10 women who suffered from intractable seizures despite high therapeutic doses of carbamazepine, phenytoin, phenobarbital and valproic acid, in monotherapy or combined, with triptorelin. Three women became seizure free within 12 months of follow-up, four had a reduction of seizure frequency up to 50%, and the duration of seizures were shortened in one patient while the two remaining patients did not experience any beneficial effect [72]. Treatment over the same time period with goserelin reduced hospital admissions from ten to three in a woman with frequent catamenial status epilepticus despite therapeutic AED levels [73]. It has been also reported that seizures frequency increases in the perimenopause in women with CE, most probably due to a reduced progesterone elevation in the luteal phase, more anovulatory cycles, and a change in the estrogen/ progesterone ratio [63]. Interestingly, seizure frequency increased as well in menopausal women which are under *hormone replacement therapy* (HRT) with conju-

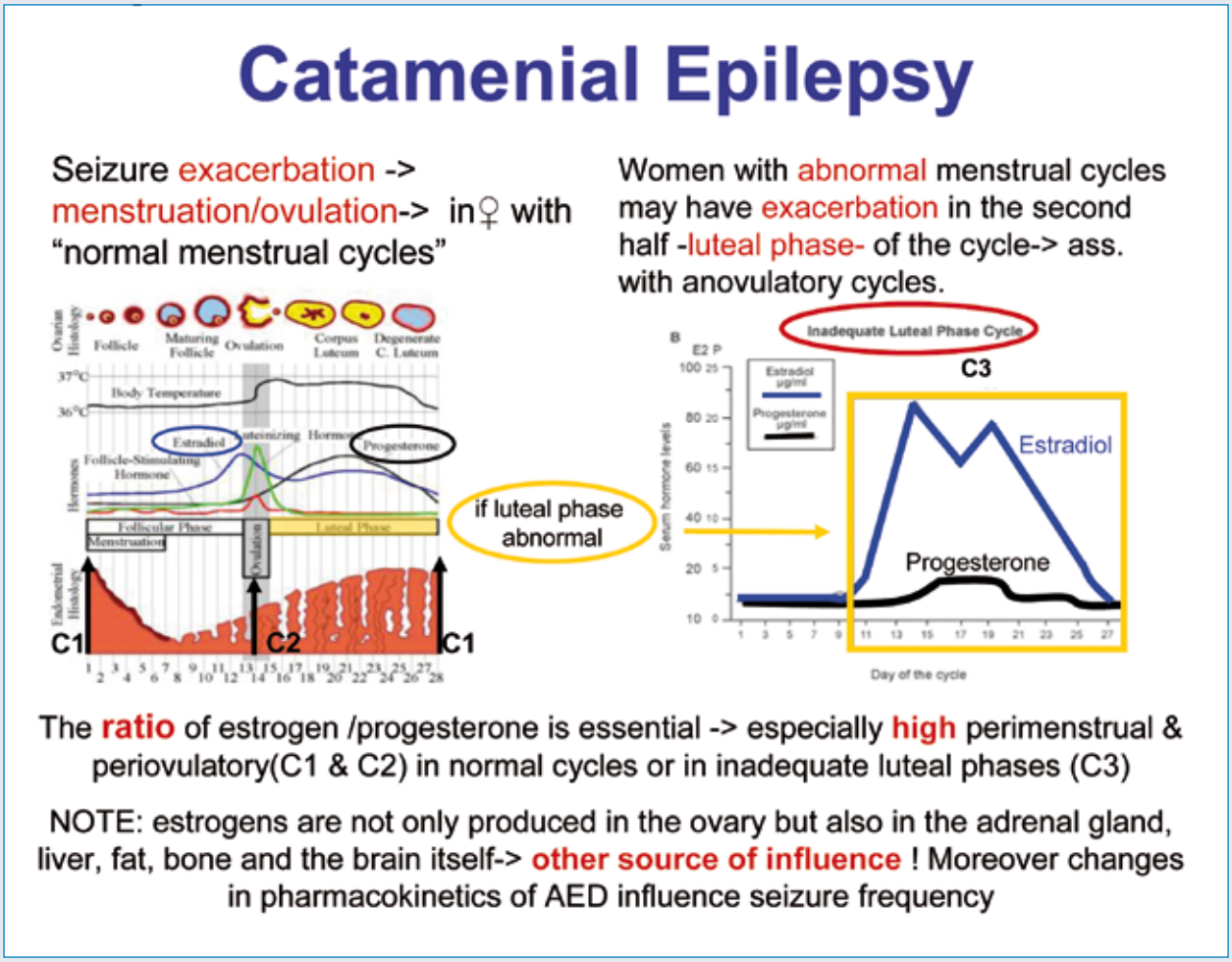


Figure 3: The term "catamenial epilepsy" is commonly used for women in whom seizures cluster in relation to the menstrual cycle. The three patterns of catamenial exacerbation of epilepsy in relation to serum estradiol and progesterone levels are abbreviated: C1= perimenstrual; C2= periovulatory; C3= throughout the second half of the menstrual cycle in women with an inadequate luteal phase (anovulatory cycles -> no corpus luteum-> no progesterone increase).

gated equine estrogens (CEE) and medroxyprogesterone acetate (MPA) [74]. The lack of a protective effect of MPA results probably from its pharmacology because MPA is not metabolized into allopregnanolone which is the most potent anticonvulsant metabolite of natural progesterone by acting at the GABA-A receptors. These results still demonstrate the importance of appropriately adapted AED during peri-menopause and menopause, especially, if the women are taking HRT.

Testosterone seems to have mixed effects on seizures. Testosterone-related seizure exacerbation has been attributed to the effect of its metabolites, estradiol (rather pro-convulsive effects) and 3α-androstanediol, which influences ictal activity by GABA-A receptors, opens chloride channels, repolarises neuronal membranes leading to an inhibition of firing action potentials [3, 75-77]. Further testosterone metabolites (dihydrotestosterone) decrease the excitability of glutamateergic neurons [38]. It has been shown that the administration of androgens can reduce ictal activity in animal models [3]. In clinical studies, alcoholic men with lower testosterone levels experience more seizures when compared to those with relatively higher levels [3]. Androgen treatment reduced seizure frequency in young men with posttraumatic seizures [78]. Testosterone supplementation (with or without an aromatase inhibitor (anastrozole)) for hypogonadal men with epilepsy led to an improvement in sexual functions and significantly decreased seizure activity [78-80]. Nevertheless, hormone treatment in epilepsy is still under investigation and patients should be selected carefully.

Epileptic activity and its impact on gonadal hormones

Patients with epilepsy, women and men, suffer more often from reproductive dysfunction than the average population of similar age [81, 82]. Sexual disorders are observed in 30%-50% of patients with epilepsy [83, 84]. This results from several causes and complex multifac-

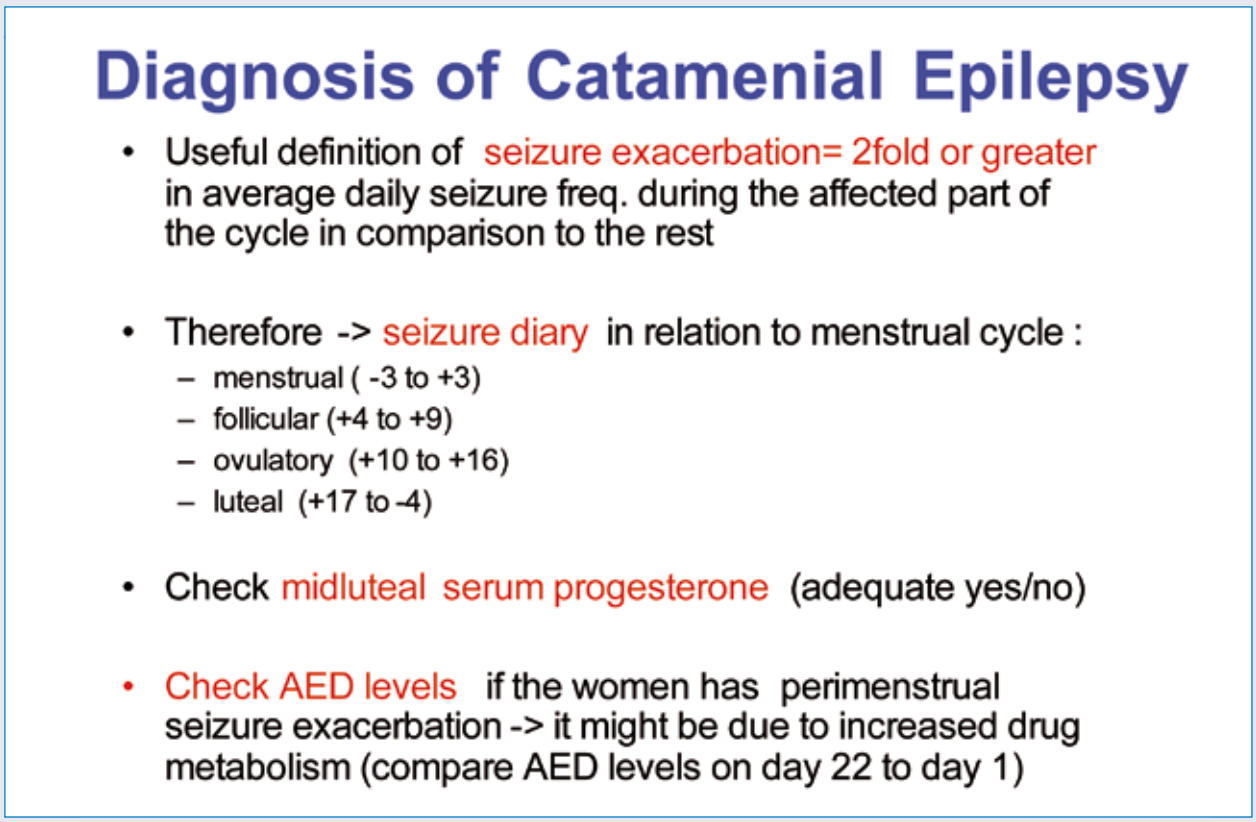


Figure 4: Important aspects for the diagnosis of catamenial epilepsy

tions in a network involving neurological, endocrine, iatrogenic and psychosocial factors [59]. Reproductive dysfunction generally manifests as menstrual disorders, hirsutism, diminished arousal, anorgasmia, and infertility in women [85] and loss of libido, impotence, and infertility in men [81]. In this context, ictal and interictal paroxysmal epileptic discharges contribute to the disruption of GnRH pulsatility [86, 87]. Reproductive dysfunction are typically seen in temporal lobe epilepsy (TLE), but also in patients with idiopathic generalized epilepsy (IGE) syndromes [59].

Women with TLE have menstrual cycle abnormalities in about 60% of cases, and include amenorrhea, oligomenorrhea or abnormally long or short menstrual cycle intervals. These abnormalities are often associated with distinct reproductive endocrine disorders [85]. Two of these disorders are polycystic ovary syndrome (PCOS) and hypothalamic hypogonadism (HH). Polycystic appearing ovaries (PCAOs) have been found in 26% of women with localization-related epilepsy and in 41% of women with IGE syndromes, significantly more than in the control group where only 16% had PCAOs [88].

Hyposexuality is also seen more often in women with (especially temporal lobe) epilepsy than in the general population, most likely due to epilepsy-related dysfunction, but also due to psychosocial stress factors and medications (estimated in 25-65%) [89]. The fertility of married women with TLE is markedly impaired in comparison to that of the general female population which is reflected by a reduction of 69% to 85% in the expected number of offsprings [89, 90].

More than one third of menstrual cycle's in women with localization-related epilepsy are anovulatory (normally 8-10%) and these cycles in turn are known to be associated with increased seizure frequencies which may lead to a vicious circle [91-94].

The underling *pathogenic* mechanism of these disorders has not been fully elucidated. It may relate to the effect of mainly temporal lobe seizures and/or epileptiform discharges upon functioning of the hypothalamo-pituitary-gonadal-axis. Projections from the temporal lobe, the diencephalon and the amygdala may influence neurosecretatory cells and their pulsatile secretion of GnRH. Gonadal steroids, in turn, bind via feedback mechanisms to receptors especially of the amygdala and influence neuronal activity. The amygdala can be divided in 2 parts, the corticomedial which stimulates gonadotropin function and ovulation and the basolateral which inhibits gonadotropin function and ovulation. In addition, it seems that also laterality plays a role. Discharges derived from the left amygdala lead to an increase in luteinizing hormone releasing hormone (LHRH) while discharges issued from the right amygdale lead to a reduced LHRH activity (summarized from [85, 95-104]; see also **Figure 5**).

Men with epilepsy also suffer from increased sexual dysfunction [105] including hypo- and hypergonado-

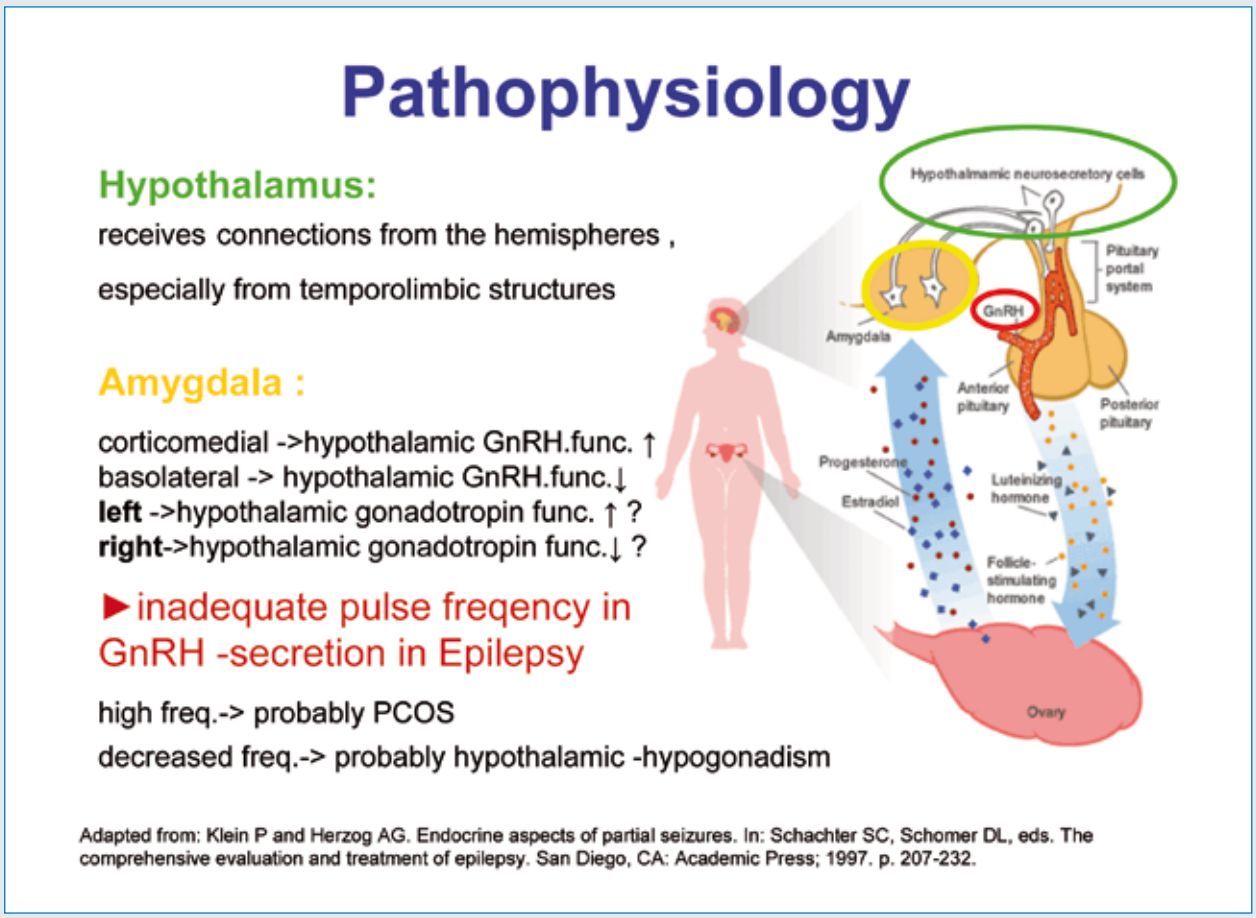


Figure 5: Projections from the temporal lobe, the diencephalon and the amygdala may influence neurosecretatory cells and their pulsatile secretion of Gonadotropin Releasing Hormone (GnRH). Gonadal steroids in turn bind to receptors especially of the amygdala and influence neuronal activity via feedback mechanisms. The amygdala itself can be divided into 2 parts, the corticomedial which stimulates gonadotropin function and ovulation, and the basolateral which inhibits gonadotropin function and ovulation. In addition, it seems that also laterality plays a role. Discharges derived from the left amygdala lead to an increase in luteinizing hormone releasing hormone (LHRH) while discharges issued from the right amygdale lead to a reduced LHRH activity.

tropic hypogonadism (about 25 and 10%, respectively), and hyperprolactinemia (about 10%) [81]. The most common dysfunction is hyposexuality which is present in one- to two-thirds of all men with TLE [81]. Elevated interictal prolactin levels may additionally contribute to hyposexuality in these patients. It is also believed that epileptic activity modulates the frequency of LHRH pulses in men [86]. Men with TLE have lower levels of free testosterone and albumin-bound testosterone, as well as increased levels of estrogen, sex hormone binding hormone globulin (SHBG), follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin [59, 85]. Interestingly, curing temporal lobe epilepsy by surgery leads to a normalization of testosterone levels [106].

Antiepileptic drugs and hormone metabolism

Beyond the effects of epilepsy itself, AEDs can target a number of substrates affecting hormone levels, including peripheral endocrine glands, liver and the adipose tissue. The clinically most prominent and relevant effects of anticonvulsant medications on endocrine function are those on sexuality and reproductive functions [107, 108]. Antiepileptic drugs may also influence mood and modulate sexual behaviour in women and men. *Enzyme-inducing AEDs* (e.g. Phenobarbital (PB) , *phenytoin* (PHT) and *carbamazepine* (CBZ)) elevate SHBG inducing a decrease of free gonadal steroids [107] in men and women.

Enzyme-inhibitors, like valproic acid, can provoke weight gain and hyperandrogenism by inhibition of the conversion of testosterone to estradiol. This increases also the risk for PCOS in women and can provoke hyperinsulinism [59, 109]. Carbamazepine might be beneficial for women with hyperandrogenism [110]. Sub-

stitution of valproic acid (VPA) with lamotrigine might result in normalization of elevated serum testosterone levels and menstrual cycles.

Valproic acid, CBZ and PHT act directly on the testis and inhibit testosterone synthesis in men. In addition, CBZ and VPA affect testosterone feedback on LH. Chronic use of CBZ and PHT leads to elevated SHBG levels and also decreased bioactive free testosterone levels in men. However, oxcarbazepine (OXC), although a weak enzyme-inducing AED at high doses, has only little or less than other AEDs effect on reproductive function in man (paragraph summarized from [109, 111, 112]). Notably, some AEDs may alter the metabolism of testosterone to estradiol and/or dihydrotestosterone or 3α-diol [38, 113]. Levetiracetam has been shown to increase testosterone levels in men with epilepsy [114]

Concerning *contraception* and the use of AED, it is important to note that enzyme inducing AEDs reduce the effectiveness of all hormonal contraception which contain estrogens. These AEDs provoke an induction (via cytochrome P-450) of the liver metabolism of estrogen/progestins as well as an increase in SHBG which in turn results in a reduction of biologically active circulating hormones [107]. Therefore, it is recommended to use another contraception method or to change AEDs (to e.g. gabapentin, lamotrigine, levetiracetam, tiagabine, valproate, and zonisamide). If oral contraceptives containing estrogenes are used, it is important to note that they reduce lamotrigine levels (two- to threefold change in serum lamotrigine levels [115]).

Most AED levels decrease during *pregnancy* due to malabsorption, decreased plasma protein binding, increased medication clearance and noncompliance because of the fear to induce congenital malformations. Good clinical practice advises to measure biologically active levels of AEDs before conception (baseline) and then every trimester [110]. More frequent monitoring in women using lamotrigine is recommended given its markedly increased clearance during pregnancy [116]. In the first four weeks post partum close monitoring of AED levels should also be performed, because pregnancy-associated alterations of metabolism and protein-binding, as well as gestational hydremia quickly remit and AED levels subsequently may become relatively rapidly toxic if not appropriate adaptations (reductions) are made.

As in most patients with epilepsy who have been seizure-free for at least 2 - 5 years, have a normal electroencephalogram, and a normal clinical examination, AED withdrawal can be considered in women with epilepsy who wish to become pregnant [117]. The risk of recurrent seizures is cumulative, but greatest within the first 6 months of discontinuing AEDs; therefore, conception should not be planned for at least 6 months after complete withdrawal of AEDs [110, 117].

Conclusion

Epilepsy, antiepileptic drugs and gonadal hormones have complex interactions. Hormones may alter seizure threshold, and change frequency and severity of seizures. In turn, epilepsy and/or antiepileptic drugs can compromise the reproductive hormonal and sexual functions in women and men. A better understanding of hormone-brain interactions should promote a variety of innovative approaches to an improved treatment of epilepsy through both behavioural and pharmaceutical interventions.

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