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HORMONAL BACKGROUND IN YOUNG MEN WITH EPILEPSY: THE INFLUENCE OF PATHOLOGY AND TREATMENT

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The study examined the effect of some antiepileptic medications and the disease itself on the hormonal background of young men.

The aim of the study was to examine the effect of some antiepileptic drugs and the disease itself on the hormonal background of young men.

Methods: This study involved 80 male patients aged 18-44 years. All patients were divided into 4 groups depending on the monotherapy received: carbamazepine (CBZ), valproic acid (VA), levetiracetam (LEV) and oxcarbazepine (OXC). Twenty healthy males aged 18-44 years (31.30 ± 4.07), who met the inclusion criteria, were included in the study as a control group. Venous blood samples (5 mL) were collected in heparinized tubes between 07:00 and 08:00 am after a fasting period of 8 hours for measurement of serum hormones. The levels of estradiol, progesterone, testosterone, and prolactin were determined by chemiluminescence analysis.

Results: epilepsy and sexual hormones abnormalities are strictly linked. Moreover, the use of many ASMs (in particular, CBZ, VPA, LEV and OXC) can contribute to these abnormalities in men with epilepsy. Over time, these alterations may result in diminished potency and fertility.

Conclusions: the ASMs' therapy may lead to dysregulation of sex hormones and sexual dysfunction in male patients with epilepsy. The use of the liver enzyme inducing AEDs, such as carbamazepine, which increases serum sex hormone binding globulin (SHBG) concentrations. This increase leads to diminished bioactivity of testosterone, which may result in diminished potency and thus reduced fertility. Men taking valproic acid have significantly higher dehydroepiandrosterone levels and lower gonadotropin concentration. This must be considered for the selection of antiepileptic drugs in young male patients. However, the effect of both the disease itself and ASMs' therapy on hormones in young men requires further research

Keywords: epilepsy, testosterone, progesterone, prolactin, estradiol, relationship, young men, treatment, antiseizures medications, carbamazepine, valproic acid, levetiracetam, oxcarbazepine

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1. Introduction

Epilepsy is one of the actual medical and social problems. Currently, according to the International League Against Epilepsy (ILAE), at least 75 million people in the world suffer from epilepsy. According to WHO, about 2.5 million new cases are diagnosed worldwide each year. The overall incidence of epilepsy is 61.4 per 100,000 person-years (95 % CI 50,7–74,4) [1]. The incidence of this pathology is higher in low-income countries than in high-income countries 139.0 (95 % CI 69.4–278.2) versus 48.9 (95 % CI 39.0–61.1). This could be explained by the different risk group structure and greater exposure to perinatal risk factors, higher rates of central nervous system (CNS) infections and traumatic brain injuries (TBI) in low/middle-income countries. The prevalence of epilepsy in Ukraine ranges from 50 to 73 cases per 100,000 population (an average of 73.9 per 100,000).

10 % of people around the world have had an attack of loss of consciousness at least once in their lives, but a single paroxysm is not a reason for diagnosis.

Epidemiological studies show that the prevalence of epilepsy in men is higher than in women. The average incidence in men (53.7 per 100,000) is slightly higher than in women (46.3 per 100,000) [2]. About 38 %–71 % of men with epilepsy have sexual dysfunction, and fertility rates are only one-third to one-half of the rate in healthy people.

The brain regulates hormonal secretion and is sensitive to hormonal feedback; the neuroendocrine feedback system includes the hypothalamus, pituitary gland, gonads, and amygdala, which is connected to the hypothalamic–pituitary axis [3] (Fig. 1), involved in the regulation, production, and secretion of sex hormones.

The interaction between hormones, epilepsy and antiseizures medications (ASMs) is complex. How hormones affect epilepsy is also obvious, epileptiform activity affects hormones. In addition, ASMs can disrupt endocrine function. Epilepsy and ASMs can affect various substrates, affecting hormone levels. The clinical importance of these interactions is primarily related to the effect on reproductive hormones.

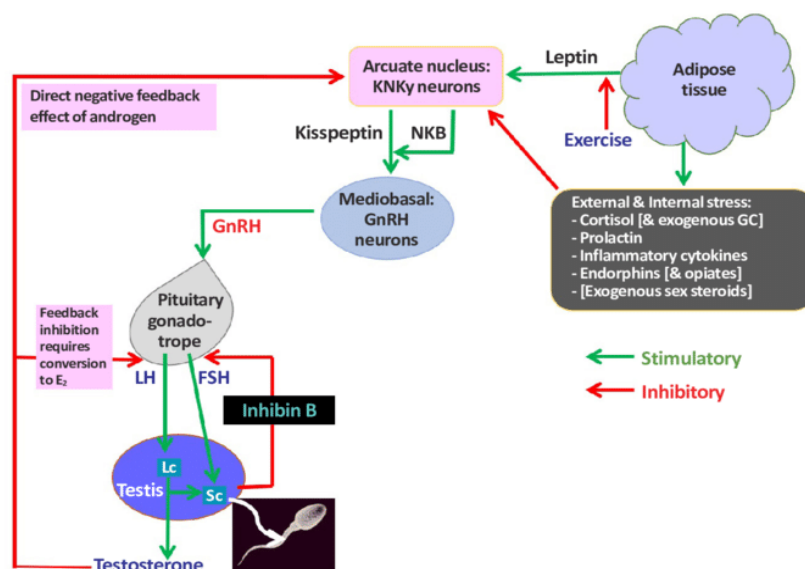


Fig. 1. Male hypothalamic-pituitary-gonadal axis

Estradiol

Estrogens do affect the GABAergic system over time. Prolonged exposure (more than 24 hours) to estradiol suppresses GABAergic inhibition of hippocampal neurons that may be related to decreased GABA release at inhibitory synapses [4]. It is assumed that estradiol decreases GABA synthesis by reducing the activity of glutamate decarboxylase (GAD) [5–7].

Estradiol has also been found to alter brain morphology by increasing the density of dendritic spines through an NMDA-receptor-dependent mechanism and altering the structure of the hippocampal synaptic connection. Estradiol selectively increased the sensitivity of neurons to synaptic input mediated by NMDA glutamate receptors, while responses mediated by AMPA receptors were not affected. These permanent, plastic changes in morphology associated with the density of roots and the sensitivity of neurons to glutamate are of great importance in relation to the effect of estrogens on the excitability of the brain.

Progesterone

The main mechanisms by which progesterone and its metabolites exert their influence on the excitability of the brain are non-classical and are associated with membrane receptors. Progesterone receptors are widely distributed in the brain [8], and progesterone circulating in the blood gets fast and relatively unrestricted access to all parts of the nervous system [9, 10]. Nerve tissue could convert progesterone into more powerful antiepileptogenic metabolites of progesterone in the brain.

The main effects of progesterone and its metabolites are associated with an increase in the postsynaptic gabaergic effect. The binding site of progesterone and its metabolites in the GABA receptor complex is unique and differs from the binding site of both barbiturates and benzodiazepines. Progesterone and its metabolites can also affect the mechanisms of arousal. Both progesterone itself and several of its metabolites, including 3α - 5α -THP, reduce sensitivity to glutamate after systemic or topical use [11–13].

Progesterone may diminish human cortical excitability. Epileptic spike frequency was decreased in men.

This effect was most prominent in those patients with the lowest progesterone-binding capacity, suggesting that the effect is related to the free, biologically active progesterone fraction.

Although the effect on non-classical mechanisms is certainly most important for the role of progesterone and its metabolites as anticonvulsants, a possible effect on intracellular, classical progesterone receptors cannot be completely excluded.

Prolactin

Prolactin is synthesized in the anterior pituitary lobe and regulated via the infundibular dopamine pathway. Prolactin levels may increase because of stimulation of the hypothalamus after abnormal discharge of neurons in patients with epilepsy.

S. Banerjee et al. [14] noted a particularly high level of prolactin after the end of generalized tonic-clonic and focal seizures. The maximum concentration was observed at the 10th minute after their completion, and the initial level was established only by the 100th minute. A high level of prolactin after the end of seizures could serve as an indicator of a high risk of recurrent generalized and focal seizures.

The rise in the level of postictal prolactin could be considered in the differential diagnosis of epileptic and non-epileptic seizures: a twofold increase in its level is a marker of epileptic seizures and allows differentiating them from psychogenic non-epileptic seizures.

Inhibitors of prolactin secretion will show antagonism towards seizures, and stimulants, on the contrary, have a proconvulsive effect.

Testosterone

ASMs have multiple effects on the metabolism of sex hormones. For example, an increase in the concentration of SHBG (sex hormone binding globulin) was observed in men with epilepsy during therapy with enzyme-inducing antiepileptic drugs such as phenytoin, phenobarbital and carbamazepine [15]. Over time, such an increase in SHBG in serum leads to a decrease in free testosterone and estradiol through increased binding to proteins, reducing serum concentrations of sex steroids, which leads to a decrease in potency in men. There was

also a significant decrease in luteinizing hormone (LH), estradiol and prolactin. In addition, reproductive hormones have a great influence on the excitability of neurons and, consequently, on epileptic seizures. This is confirmed by both clinical observations and experimental animal studies.

Bioactive testosterone is abnormally low in men with epilepsy, and they often suffer from reproductive disorders.

Epilepsy itself is an endocrine disruptor and leads to hypothalamic dysfunction, which, in turn, usually has the opposite effect on the concentration of androgens in young men, i.e., androgen activity decreases. The effect of epilepsy on central reproductive activity is complicated by metabolic changes caused by ASMs on reproductive hormones.

Also, these diseases can coexist independently of each other, i.e., they can be comorbid, aggravating the course of each pathology and worsening the quality of life and prognosis for the patient as a whole.

The effect of ASMs on hormones

Some ASMs have a direct effect on the production of sex steroid hormones.

ASMs cause inhibition of the synthesis of free testosterone by direct action on the testicles or reduce the level of free testosterone by increasing the level of sex hormone binding globulin and serum estradiol because of the induction of the enzyme.

In fact, circulating levels of carbamazepine, an enzyme-inducing ASM, enhances testosterone metabolism, so that bioavailable testosterone is suppressed, but testosterone aromatized and 5-reduced (e.g., dihydrotestosterone) metabolites are increased.

Oxcarbazepine (OXC), a keto derivative of CBS, is a novel ASM that is structurally very similar to CBZ [16]. It has a different metabolic pathway in the liver: instead of oxidation, it is mainly metabolized by reduction and does not appear to cause an oxidative P450 enzyme system [17].

Unlike carbamazepine, oxcarbazepine has practically no effect on hormones.

The effect of oxcarbazepine on reproductive endocrine function in men is dose-dependent: in doses up to 900 mg / day. the concentration of male sex hormones in the blood does not change, in higher doses there is an increase in the level of testosterone, gonadotropins, binding globulin. Oxcarbazepine does not cause a decrease in the bioactivity of androgens [18]. OXC may be associated with an increased frequency of morphologically abnormal spermatozoa in men with epilepsy [19].

Valproic acid is the enzyme inhibitor of ASMs. Using concentrations from 600 to 1500 $\mu\text{mol/l}$ VPA, which includes clinically relevant concentrations, it was shown that VPA increased the secretion of testosterone, decreased estradiol secretion, and reduced the conversion of testosterone to estradiol. VPA was demonstrated to cause a significant increase in LH-stimulated testosterone secretion and a decrease in FSH-stimulated estradiol secretion. Further, VPA reduced CYP19 aromatase activity in FSH-stimulated cells at higher concentrations [20].

Levetiracetam (LEV) binds to the synaptic vesicle protein, SV2A. SV2A is widely distributed in the nervous system and also in endocrine tissue. LEV may exert its

effect both at the central and peripheral level as SV2A is expressed in the pituitary gland and the hypothalamus [21].

The aim of the study was to examine the effect of some antiepileptic drugs and the disease itself on the hormonal background of young men.

2. Materials and methods

The study was conducted based on the State Institution “Kharkiv Medical Academy of Postgraduate Education of the Ministry of Health of Ukraine” for the period 2019–2021.

Ethical aspects. The work complies with the ethical standards of the Declaration of Helsinki by the World Medical Association. A written informed consent was obtained authorizing the publication of the medical history and the results of the examination.

The work was carried out the protocol of the Bioethics Commission of the “Kharkiv Medical Academy of Postgraduate Education” No. 1 dated 10.02.2022 were followed.

This study involved 80 male patients aged 18–44 years. According to the WHO classification, all subjects belonged to the group of young people. The average age of the patients was 32.73 ± 7.23 .

All patients were divided into 4 groups depending on the monotherapy received: carbamazepine (CBZ), valproic acid (VPA), levetiracetam (LEV) and oxcarbazepine (OXC). Patients included in the study were monotherapy for 6 months or more. Age at onset of epilepsy seizures and types and number of seizures of the patient groups were recorded from the patient files. According to the ILAE operational classification of seizure types, all seizures were grouped as focal onset with aware or impaired awareness, generalized and unknown onset (Table 1).

Table 1

Average age (M \pm Sd) of groups	
Medication group	Age, yrs
CBZ group	28.62 \pm 8.11
VPA group	30.73 \pm 9.96
LEV group	31.62 \pm 8.73
OXC group	29.70 \pm 6.18
Control group	31.30 \pm 4.07

Note: CBZ – carbamazepine; VPA – valproic acid; LEV – levetiracetam; OXC – oxcarbazepine

The study did not include men with significant somatic pathology, acute and chronic, as well as with brain tumors, acute traumatic brain injuries and acute infectious diseases of various etiologies, as well as patients who received hormone therapy.

Twenty healthy males aged 18–44 years (31.30 ± 4.07), who met the inclusion criteria, were included in the study as a control group.

Venous blood samples (5 mL) were collected in heparinized tubes between 07:00 and 08:00 am after a fasting period of 8 hours for measurement of serum hormones. The levels of estradiol, progesterone, testosterone, and prolactin were determined by chemiluminescence analysis.

Statistical analysis. The STATISTICA 13.0, Stat Soft Inc. (USA) and Microsoft Excel XP application

software package was used for statistical analysis. The data were expressed as an average standard deviation when the quantitative data corresponded to a normal distribution, and the Student's t-test was carried out for analysis. For quantitative data that did not correspond to the normal distribution, the Mann-Whitney test was used, and the component coefficients were determined using the Pearson criterion (χ^2) or the Fisher exact criterion.

3. Result

There was no significant age difference between patients receiving VPA, CBZ, LEV, OXC and the control group. The average age of onset of seizures was 17.87±9.28 years in the CBZ group, 19.71±12.53 – in the VPA group, 18.69±11.32 – in the LEV group, 19.53±7.68 years – in the OXC group. Data of the patients are provided in Table 2.

Table 2

Clinical features of groups		
Medication group	Age at first seizure, yrs	Duration of epilepsy, yrs
CBZ group	17.87±9.28	10.84±10.04
VPA group	19.71±12.53	11.01±7.26
LEV group	18.69±11.32	9.76±10.24
OXC group	19.53±7.68	11.20±6.96

Note: CBZ – carbamazepine; VPA – valproic acid; LEV – levetiracetam; OXC – oxcarbazepine

Several clinical studies have reported that patients treated with AEDs had elevated plasma homocystein (Hcy) levels. It is well known that folate deficiency occurs in some epileptic patients taking AEDs such as valproate and carbamazepine, and this effect could induce hyper-Hcy. Although the mechanisms by which AEDs induce folate depletion are still unclear, the proposed mechanisms can be summarized as interference with the intestinal absorption of folate, induction of enzymes in the liver and finally depletion of folate, and

interference with the metabolism of folate co-enzymes. Elevated plasma Hcy level may be an independent risk factor for erectile dysfunction. In fact, Hcy promotes oxidant injury to the vascular endothelium, impairs endothelium dependent vasomotor regulation, and may also alter the coagulant properties of blood. Impaired endothelial function and the consequent decreased capacity of the vascular smooth muscle to relax are regarded as precursors of atherosclerosis and subsequent impaired cavernosal perfusion (Table 3).

Table 3

Change of hormones' levels in male epileptic patients					
Medication group	CBZ group	VPA group	OXC group	LEV group	Control group
Name of the hormone					
Prolactin	N	↑	N	↑	N
Estradiol	↑	↑	N	↓	N
Progesterone	↑	↑	↑	N	N
Total testosterone	↑	↓	↑	N	N

Note: CBZ – carbamazepine; VPA – valproic acid; LEV – levetiracetam; OXC – oxcarbazepine; N – normal; ↑ – increased; ↓ – decreased.

The Table 3 shows how the hormone levels of each group changed depending on the ASMs monothera-

py compared to the control group of young men. Hormone test results are shown in Table 4.

Table 4

Serum hormone concentrations in patients who were treated with valproic acid (VPA), carbamazepine (CBZ), oxcarbazepine (OXC) or levetiracetam (LEV) for epilepsy, and in control group

Hormone	Medication group	Mean±SD	P
Prolactin, mIU/L	CBZ group	221.60±76.20	>0.05
	VPA group	229.00±67.20	>0.05
	OXC group	219.90±77.50	>0.05
	LEV group	225.50±71.30	>0.05
	Control group	220.80±77.00	>0.05
Estradiol, pmol/L	CBZ group	157.60±11.60	>0.05
	VPA group	156.90±18.00	>0.05
	OXC group	155.70±10.00	>0.05
	LEV group	150.60±11.60	>0.05
	Control group	155.30±10.40	>0.05
Progesterone, ng/mL	CBZ group	2.27±2.22	<0.05
	VPA group	3.11±2.48	<0.05
	OXC group	2.19±2.31	<0.05
	LEV group	1.89±1.02	>0.05
	Control group	1.83±0.88	>0.05
Total testosterone, ng/mL	CBZ group	7.60±1.70	>0.05
	VPA group	3.30±1.90	<0.01
	OXC group	7.40±1.80	>0.05
	LEV group	6.60±1.90	<0.05
	Control group	6.60±1.90	<0.05

Note: CBZ – carbamazepine; VPA – valproic acid; LEV – levetiracetam; OXC – oxcarbazepine. The indicators of CBZ group, VPA group, OXC group and LEV group were compared with the indicators of the control group

According to the data given in the Table 4, the prolactin levels were higher in young men taking VPA or LEV compared to the control group.

Testosterone levels were significantly lower in the VPA group compared to the control group.

Estradiol levels were high in the VPA and CBZ groups compared to the control group.

4. Discussion

The potential effect of epilepsy on endocrine and reproductive functions has been considered in many studies. In recent years, the effects of enzyme inducing ASMs (EIAEDs) on androgen metabolism have been invoked as a possible etiologic factor.

Sex hormones are actively metabolized in the liver by the enzymatic system of the cytochrome P450 oxidase family. However, there is no consensus on changing hormone levels.

Kuba et al. [22] showed that estradiol levels were high in male epileptic patients taking CBZ.

During this study, it was found that men who took CBZ had higher estradiol levels compared to the control group. Thus, once again confirming the previously obtained data.

Reis RM et al reported that the levels of prolactin and testosterone were normal in epileptic patients taking CBZ, and CBZ might lead to sexual dysfunction by different pathophysiological mechanisms [23].

The data obtained after this study partially coincide with the information presented above. However, in young men taking CBZ, only prolactin levels were within the normal range. While the testosterone level was increased in comparison with the control group.

VPA is an inhibitor of UGT enzyme system including UGT2B15, which involves in androgen and estrogen metabolism. It is thought that VPA can increase testosterone and estradiol levels by inhibiting sex steroid metabolism [24].

The increase in estradiol levels in young men taking VPA was observed in comparison with the control group, while testosterone levels were reduced. The results obtained partially confirm the previously research data.

The recent clinical study has also shown that VPA may reduce sperm motility, increase the frequency of morphologically abnormal sperm, and be associated with small testicular size in men with epilepsy [25].

Study limitations. The study was not conducted in case of identified concomitant pathology of other organs and regarding the patients refuse to participate in the study.

Prospects for further research. The obtained results indicate the need for further research to identify factors affecting changes in hormone levels and the course of epilepsy.

5. Conclusion

There is an intricate multidirectional interplay between epilepsy, hormones and ASMs.

There is evidence, both clinical and experimental, that hormones, particularly sex steroids, influence the probability of seizure occurrence. Sex steroids have significant actions and effects in the CNS. The action of an individual hormone is determined by specific effects on neuronal excitability and on the unique anatomic distribution of receptors for that hormone.

Epilepsy and sexual hormones abnormalities are strictly linked. Moreover, the use of many ASMs (in particular, CBZ, VPA, LEV and OXC) could contribute to these abnormalities in men with epilepsy. Over time, these alterations may result in diminished potency and fertility.

Hormonal changes and sexual dysfunction need to be addressed in comprehensive epilepsy research programs of a controlled nature, with larger samples and longer follow-up periods.

Conflicts of interests

The authors declare that they have no conflicts of interest.

Financing

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