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Mean daily plasma concentrations of β-endorphin, leu-enkephalin, ACTH, cortisol, and DHEAS in epileptic patients with complex partial seizures evolving to generalized tonic-clonic seizures

Średniodobowe stężenia β-endorfiny, leu-enkefaliny, ACTH, kortyzolu i DHEAS w osoczu chorych na padaczkę z napadami częściowymi złożonymi i wtórnie uogólnionymi toniczno-klonicznymi

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Abstract

Introduction: A multitude of mechanisms have been implicated in the pathophysiology of epilepsy. Objective: To assess mean daily plasma concentrations of ACTH, cortisol, DHEAS, leu-enkephalin, and beta-endorphin in epileptic patients with complex partial seizures evolving to tonic-clonic in relation to frequency of seizure occurrence (groups with seizure occurrences — several per week and several per year) and duration of the disease (groups less than and more than 10 years). We decided to analyse mean daily values of beta-endorphin and leu-enkephalin because of significant differences in concentrations of these substances in blood during the day.

Material and methods: The study was performed on 17 patients (14 males + 3 females; mean age 31.8 yrs) treated with carbamazepine (300–1800 mg/day). The control group consisted of six age-matched healthy volunteers. Blood was collected at 8 a.m., 2 p.m., 8 p.m., and 2 a.m. Intergroup analysis was performed with the use of ANOVA Kruskal-Wallis test.

Results: Mean daily concentrations of ACTH and cortisol in the blood of the patients with epilepsy were higher in comparison with those of the healthy volunteers, independently of the frequency of seizures and duration of the disease. Mean daily concentrations of beta-endorphin in the blood of the patients with epilepsy were higher in the groups of patients with more severe clinical course of disease (with more frequently occurring epilepsy seizures and longer duration of the disease) in comparison with healthy subjects. Mean daily concentrations of leu-enkephalin in the blood of the patients with epilepsy were higher in the group of patients with short duration of the disease in comparison with the group with long duration of the disease.

Conclusions:

1. Pituitary-adrenal axis hyperactivity is observed in patients with clinically active epilepsy, independently of the frequency of seizures and duration of the disease.
2. Changes in endogenous opioid system activity are related to the clinical activity of epilepsy — beta-endorphin concentrations are connected with frequency of seizures and duration of the disease and leu-enkephalin concentrations with duration of the disease.
3. Endogenous opioid peptides might take part in the neurochemical mechanism of human epilepsy.

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Key words: *epilepsy, ACTH, endorphin, enkephalin, cortisol, DHEAS, endogenous opioid peptides, endogenous opioids*

Streszczenie

Wstęp: W patofizjologii padaczki uczestniczy nieokreślona ilość mechanizmów. Celem pracy była ocena średniodobowych osoczowych stężeń ACTH, kortyzolu, DHEAS, leu-enkefaliny and β-endorfiny u chorych na padaczkę z napadami częściowymi, złożonymi i wtórnie uogólnionymi, toniczno-klonicznymi w zależności od częstości napadów (grupy z częstością napadów — kilka na tydzień i kilka na rok) i od czasu trwania choroby (grupy < i > 10 lat). Autorzy zdecydowali się na analizę średniodobowych wartości β-endorfiny i leu-enkefaliny z powodu wyraźnych różnic w ich stężeniu we krwi w ciągu doby.

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Materiał i metody: Badanie przeprowadzono u 17 chorych (14 mężczyzn i 3 kobiety; średni wiek 31,8 lat) leczonych karbamazepiną (300–1800 mg/dzień). Grupa kontrolna składała się z 6 zdrowych ochotników w porównywalnym wieku. Krew pobierano o godzinie 8, 14, 20, 2. W analizie międzygrupowej wykorzystano test ANOVA Kruskala-Wallisa.
Wyniki: Średniodobowe stężenia ACTH i kortyzolu we krwi chorych na padaczkę były wyższe w porównaniu ze zdrowymi niezależnie od częstości napadów i czasu trwania choroby. Średniodobowe stężenia β-endorfiny we krwi chorych na padaczkę były wyższe w grupach pacjentów z ciężkim przebiegiem klinicznym choroby (z wysoką częstością napadów i długim czasem trwania choroby) w porównaniu ze zdrowymi. Średniodobowe stężenia leu-enkefaliny we krwi chorych na padaczkę były wyższe w grupie pacjentów z krótkim czasem trwania choroby w porównaniu z grupą z długim czasem trwania choroby.
Wnioski:
1. U chorych na padaczkę, niezależnie od częstości napadów i czasu trwania choroby, dochodzi do wzmożonej aktywności osi przysadkowo-nadnerczowej.
2. Zmiany w aktywności endogennego układu opioidowego są związane z kliniczną aktywnością padaczki — stężenia β-endorfiny pozostają w związku z częstością napadów i czasem trwania choroby, a stężenia leu-enkefaliny z czasem trwania choroby.
3. Endogenne peptydy opioidowe mogą uczestniczyć w neurochemicznym mechanizmie padaczki u ludzi.
(Endokrynol Pol 2010; 61 (1): 103–110)

Słowa kluczowe: *padaczka, ACTH, endorfina, enkefalina, kortyzol, DHEAS, endogenne peptydy opioidowe, endogenne opioidy*

Introduction

Neuropsychiatric disorders are one of the main challenges in human medicine, with epilepsy being one of the most common serious disorders of the brain. Increasing evidence suggests neuropeptides, particularly opioids, play an important role in epilepsy [1, 2]. Actual knowledge in this area is still fragmentary. In the presented experiment the authors try to define the link between the proopiomelanocortin (POMC) derived peptides (ACTH, enkephalin, and endorphin) and epilepsy (type, pharmacotherapy, and duration of the disease).

A multitude of mechanisms has been implicated in the pathophysiology of epilepsy. Since the seizure phenomenon is often associated with massive electrical discharges in the brain, most if not all of the neurohumoral transmitters may be considered to have a role in either pre- or post-seizure events. The localization of endogenous opioids in the brain suggests that they are likely to be transmitter candidates for epilepsy [1–7]. Immunohistochemical and immunoassay studies indicate the presence of various types of opioid peptides in the limbic system, above all in the hippocampus, in which the presence of prodynorphin and proenkephalin derived peptides is confirmed. Changes in enkephalins and β-endorphin activity in the brain and cerebrospinal fluid in epileptic men were among the other things described [1, 3–6]. In view of the presence of peptic transporting system-1 probably playing a role in endogenous opioid transport through the blood-brain barrier [8], there is a possibility of concentration assessment of these opioids in plasma. In the transport system are saturable and non-saturable mechanisms, and the system can be influenced by several factors such as aging, drugs, or stress.

There are some reports indicating possible pro-, but most frequently anticonvulsant effects of natural opioid peptides. Endogenous opioid peptides, through increase of the seizure threshold, may take part in spontaneous arrest of seizures and, parallel to that, in the development of the postictal refractory period, in which, among other things, its cataleptic action is revealed [1, 2, 4–7, 9–13]. There are also reports indicating the anticonvulsant effect of ACTH through correction of faulty enzymatic processes in brain, changes in the intracellular-extracellular electrolyte ratios, reduction in brain water, stimulation of the adrenal gland to produce glucocorticoids and corticotrophin-releasing hormone suppression, and data indicating that a fragment of the ACTH molecule acts as a direct neurotransmitter or does so through an indirect effect on the $GABA_A$ receptor [4, 14–16]. The therapeutic effect of ACTH in humans [16] may have been caused by potentiation of nerve growth factor action [17], taking into consideration the fact that glucocorticoids increase nerve growth factor expression in the rat brain [18].

The aim of the study was the assessment of plasma concentrations of ACTH, cortisol, dehydroepiandrosterone sulphate (DHEAS), β-endorphin, and leucine enkephalin (leu-enkephalin) in patients with complex partial seizures evolving to tonic-clonic in dependence relation to frequency of seizure occurrence (groups with seizure occurrences — several per week and several per year) and duration of the disease (groups with less than or more than 10 years). We decided to analyse mean daily values of β-endorphin and leu-enkephalin because of significant differences in the concentrations of these substances in blood during the day.

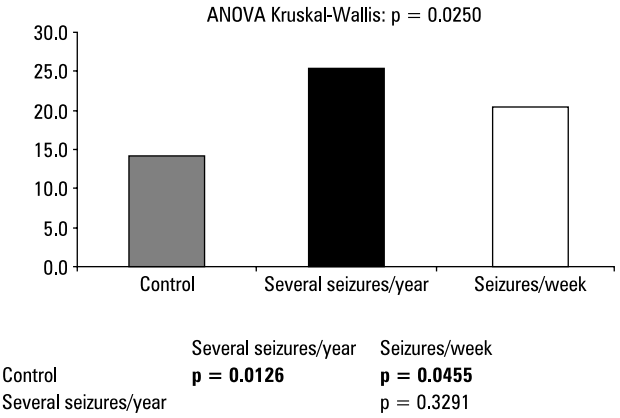
Material and methods

The study was performed on 17 patients (14 males + 3 females; mean age 31.8 ± 10.8) with complex partial seizures evolving to tonic-clonic seizures. The epileptic patients were divided according to frequency of seizure occurrence: group A — several seizures per week, group B — several seizures per year. The epileptic patients were also divided according to duration of the

Table I. *Mean daily concentrations of ACTH in the blood of patients with epilepsy in relation to frequency of seizures occurrence (groups with seizure occurrence — several per week and several per year) and in the control group*

Tabela I. *Średnie dobowe stężenie ACTH we krwi chorych na padaczkę w grupach wydzielonych w zależności od częstości napadów (kilka napadów na tydzień lub kilka napadów na rok) i w grupie kontrolnej*

ACTH [pg/ml]	Group		
	Control	Several seizures/year	Seizures/ /week
Mean	14.19	25.30	20.36
SD	1.66	9.35	5.72
SEM	0.68	2.96	2.16
N	6	10	7

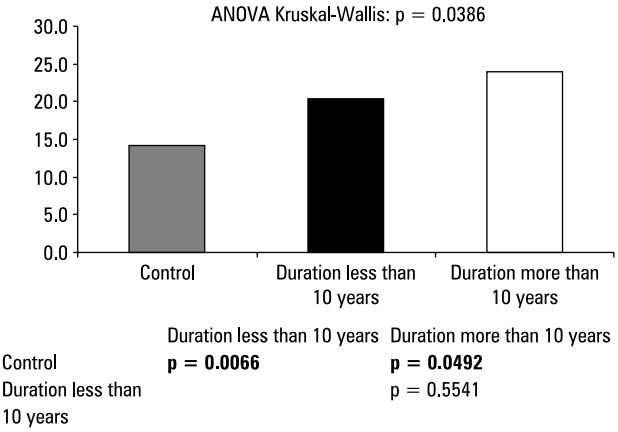


	Several seizures/year	Seizures/week
Control	**p = 0.0126**	**p = 0.0455**
Several seizures/year		p = 0.3291

Table II. *Mean daily concentrations of ACTH in the blood of patients with epilepsy in relation to duration of the disease (groups less than and more than 10 years) and in the control group*

Tabela II. *Średnie dobowe stężenie ACTH we krwi chorych na padaczkę w grupach wydzielonych w zależności od czasu trwania choroby (mniej niż 10 lat lub ponad 10 lat) i w grupie kontrolnej*

ACTH [pg/ml]	Group		
	Control	Duration less than 10 years	Duration more than 10 years
Mean	14.19	20.35	23.93
SD	1.66	3.29	9.79
SEM	0.68	1.24	2.83
N	6	7	10



	Duration less than 10 years	Duration more than 10 years
Control	**p = 0.0066**	**p = 0.0492**
Duration less than 10 years		p = 0.5541

disease: group C — duration less than 10 years, group D — duration more than 10 years. All patients were treated with carbamazepine (300–1800 mg/day). No patients with diagnosed hypothalamic, hypophyseal, or adrenocortical abnormalities were included in the study. The control group consisted of six age-matched healthy volunteers. The investigation was performed with the approval of the Local Ethics Committee, and all patients gave their written informed consent to participate in the study.

In all patients' and healthy subjects' blood was collected at 8 a.m., 2 p.m., 8 p.m., and 2 a.m. for the assessment of twenty-four-hour ACTH, cortisol, DHEAS, β-endorphin, and leu-enkephalin plasma concentrations. The plasma was frozen at –75°C until it was assayed. Concentrations of the studied compounds in plasma were assessed with the use of RIA method and commercially available kits: Cis-Bio International, Francja (ACTH); Orion Diagnostica, Finland (cortisol); DPC, USA (DHEAS); Phoenix Pharmaceuticals Inc., USA (β-endorphin, leu-enkephalin). For plasma leu-enkephalin concentration assessment, the studied samples were subjected to previous extraction with the use of ODS-silica columns (INCSTAR, USA). The sensitivity of the method amounted to: ACTH — 1 pg/ml; cortisol — 0.18 mg/dl; DHEAS — 1.1 mg/dl; β-endorphin — 0.5 pg/ml; leu-enkephalin — 0.5 pg/ml.

The obtained results were subjected to statistical analysis. Intergroup analysis was performed with the use of ANOVA Kruskal-Wallis test. The level of statistical significance amounted to $p < 0.05$.

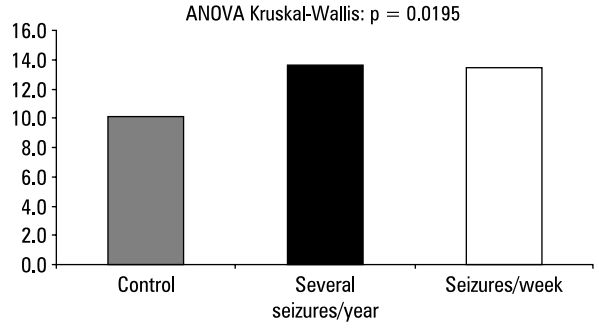
Results

In all of the analysed groups of patients with epilepsy — with low and high frequency of seizures and short and long duration of the disease — mean daily ACTH and cortisol concentrations in blood were significantly higher in comparison with the control group (Tables I–IV). No significant difference in daily secretions of ACTH and cortisol between the groups of patients with low and high frequency of seizures (Tables I, III) and between the groups of patients with short and long duration of the disease (Tables II, IV) was shown.

Table III. *Mean daily concentrations of cortisol in the blood of patients with epilepsy in relation to frequency of seizure occurrence (groups with seizure occurrence — several per week and several per year) and in the control group*

Tabela III. *Średnie dobowe stężenie kortyzolu we krwi chorych na padaczkę w grupach wydzielonych w zależności od częstości napadów (kilka napadów na tydzień lub kilka napadów na rok) i w grupie kontrolnej*

Cortisol [μg/dl]	Group		
	Control	Several seizures/year	Seizures/ week
Mean	10.09	13.65	13.44
SD	0.96	2.37	3.61
SEM	0.39	0.75	1.36
N	6	10	7

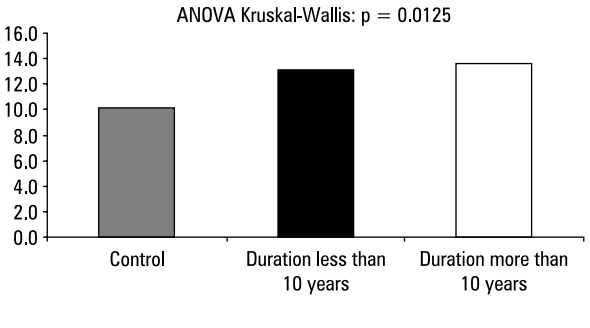


	Several seizures/year	Seizures/week
Control	**p = 0.0048**	**p = 0.0455**
Several seizures/year		p = 0.9981

Table IV. *Mean daily concentrations of cortisol in the blood of patients with epilepsy in relation to duration of the disease (groups less than and more than 10 years) and in the control group*

Tabela IV. *Średnie dobowe stężenie kortyzolu we krwi chorych na padaczkę w grupach wydzielonych w zależności od czasu trwania choroby (mniej niż 10 lat lub ponad 10 lat) i w grupie kontrolnej*

Cortisol [μg/dl]	Group		
	Control	Duration less than 10 years	Duration more than 10 years
Mean	10.09	13.09	13.64
SD	0.96	2.32	2.96
SEM	0.39	0.88	0.86
N	6	7	10



	Duration less than 10 years	Duration more than 10 years
Control	**p = 0.0101**	**p = 0.0087**
Duration less than 10 years		p = 0.4990

Mean daily DHEAS concentrations in the blood of patients with low and high frequency of seizures and long duration of the disease did not differ from those in the control group (Tables V, VI). Only in the group of patients with short duration of the disease were they significantly lower in comparison with the control group.

The mean daily concentration of β-endorphin in the blood of patients with more frequently occurring epilepsy seizures was significantly higher in comparison with the control group. However, no significant difference in daily secretion of β-endorphin between the group of patients with low frequency of seizures and the control group and between the groups of patients with low and high frequencies of seizures was observed (Table VII). In the group of patients with long duration of the disease a significant increase in β-endorphin daily secretion was noted in comparison to patients with short duration of the disease and the control group. Daily secretion of β-endorphin in the group of patients with short duration of the disease did not differ from the control group (Table VIII).

Mean daily concentration of leu-enkephalin in the blood of patients with epilepsy was significantly higher in the group of patients with short duration of the disease in comparison with the group with long duration of the disease. In all the analysed groups of patients with epilepsy — with low and high frequency of seizures and short and long duration of the disease — daily secretion of leu-enkephalin did not differ from that in the control group (Tables IX, X).

Discussion

We noticed that in patients with clinically active epilepsy, pituitary-adrenal axis hyperactivity was observed — mean daily concentrations of ACTH and cortisol in the blood of patients with epilepsy were significantly higher in comparison to healthy subjects independently of frequency of seizures and duration of the disease. We also noticed that the abnormalities in endogenous opioid system activity were related to the clinical activity of epilepsy — mean daily concentrations of β-en-

Table V. *Mean daily concentrations of DHEAS in the blood of patients with epilepsy in relation to frequency of seizure occurrence (groups with seizure occurrence — several per week and several per year) and in the control group*

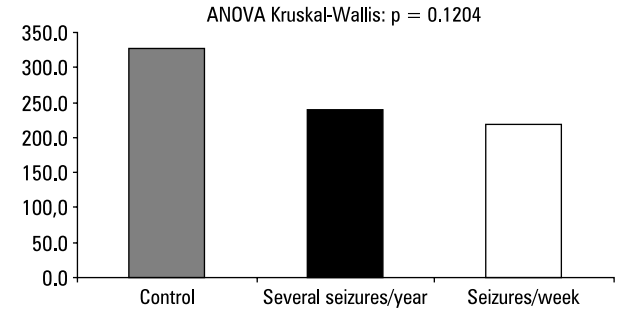
Tabela V. *Średnie dobowe stężenie DHEAS we krwi chorych na padaczkę w grupach wydzielonych w zależności od częstości napadów (kilka napadów na tydzień lub kilka napadów na rok) i w grupie kontrolnej*

DHEAS [μg/dl]	Group		
	Control	Several seizures/year	Seizures/ /week
Mean	327.55	240.36	218.98
SD	39.81	185.78	183.34
SEM	16.25	58.75	69.30
N	6	10	7

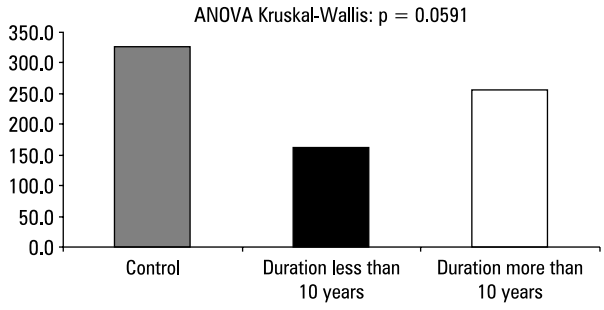
Table VI. *Mean daily concentrations of DHEAS in the blood of patients with epilepsy in relation to duration of the disease (groups less than and more than 10 years) and in the control group*

Tabela VI. *Średnie dobowe stężenie DHEAS we krwi chorych na padaczkę w grupach wydzielonych w zależności od czasu trwania choroby (mniej niż 10 lat lub ponad 10 lat) i w grupie kontrolnej*

DHEAS [μg/dl]	Group		
	Control	Duration less than 10 years	Duration more than 10 years
Mean	327.55	161.84	256.92
SD	39.81	171.41	178.92
SEM	16.25	64.79	51.65
N	6	7	10



	Several seizures/year	Seizures/week
Control	p = 0.0827	p = 0.0633
Several seizures/year		p = 0.7327



	Duration less than 10 years	Duration more than 10 years
Control	**p = 0.0321**	**p = 0.1340**
Duration less than 10 years		p = 0.1508

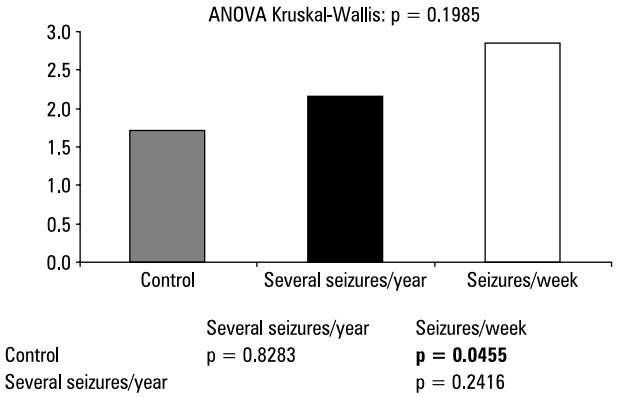
dorphin in the blood of patients with epilepsy were significantly higher in the groups of patients with more frequently occurring epilepsy seizures and long duration of the disease, and mean daily concentrations of leu-enkephalin in blood were significantly higher in the group of patients with short duration of the disease.

Except for some kinds of epilepsy (for example infantile spasms), the role of the pituitary-adrenal axis in the initial pathogenesis of epilepsy [16, 19] is rather inconspicuous. Seizures may induce hormonal changes through nervous pathways influencing the hypothalamic-pituitary function [16, 20]. Therefore, it seems that the hormonal disturbances observed by us are secondary to the basic disease (epilepsy). Physiological stress produces a number of biochemical changes in the body, including increased ACTH, cortisol, β-endorphin, and enkephalin concentrations in blood. It is therefore logical that both cortisol and β-endorphin levels in blood have been shown to rise after convulsive seizure in man [21]. Cortisol levels in blood were elevated in patients with status epilepticus who continued to have a poor outcome within the first week following seizures. In patients with status epilepticus, cerebrospinal fluid β-endorphin levels were also increased, but there was no correlation between the increase and prognosis [22]. While the significant elevation of cortisol levels associated with status epilepticus may be a reflection of the severe stress situation, the elevated cortisol level itself may be detrimental — neurons have corticosteroid receptors and corticosteroids are associated with neuronal damage and have a direct effect on neuronal activity, including their effect on catecholamine turnover and protein and energy metabolism [22, 23]. It seems that hypercortisolaemia occurring in status epilepticus with bad prognosis described by Calabrese [22] as well as in the group of epileptic patients with severe clinical course of the disease analysed by us may contribute to the pathophysiological state of the conditions. Increased cortisol values in the blood of patients with epilepsy were documented in the following reports [20, 21, 24]. It was also shown that increased secretion of cortisol was a result of increased ACTH secretion [21]. In the

Table VII. *Mean daily concentrations of β-endorphin in the blood of patients with epilepsy in relation to frequency of seizure occurrence (groups with seizure occurrence — several per week and several per year) and in the control group*

Tabela VII. *Średnie dobowe stężenie β-endorfiny we krwi chorych na padaczkę w grupach wydzielonych w zależności od częstości napadów (kilka napadów na tydzień lub kilka napadów na rok) i w grupie kontrolnej*

β-endorphin [pg/ml]	Group		
	Control	Several seizures/year	Seizures/ /week
Mean	1.71	2.16	2.85
SD	0.44	1.38	1.07
SEM	0.18	0.44	0.40
N	6	10	7

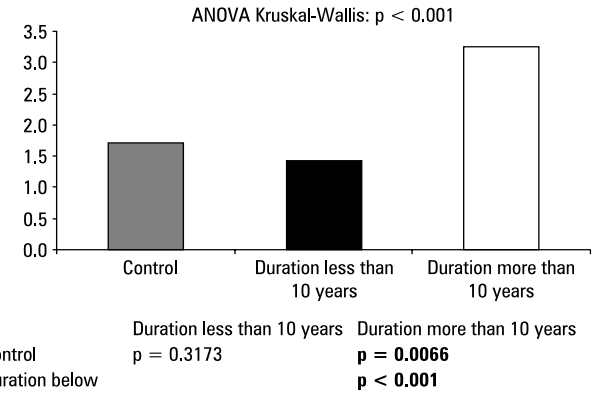


	Several seizures/year	Seizures/week
Control	p = 0.8283	**p = 0.0455**
Several seizures/year		p = 0.2416

Table VIII. *Mean daily concentrations of β-endorphin in the blood of patients with epilepsy in relation to duration of the disease (groups less than and more than 10 years) and in the control group*

Tabela VIII. *Średnie dobowe stężenie β-endorfiny we krwi chorych na padaczkę w grupach wydzielonych w zależności od czasu trwania choroby (mniej niż 10 lat lub ponad 10 lat) i w grupie kontrolnej*

β-endorphin [pg/ml]	Group		
	Control	Duration less than 10 years	Duration more than 10 years
Mean	1.71	1.43	3.25
SD	0.44	0.39	1.04
SEM	0.18	0.15	0.30
N	6	7	10



	Duration less than 10 years	Duration more than 10 years
Control	p = 0.3173	**p = 0.0066**
Duration below 10 years		**p < 0.001**

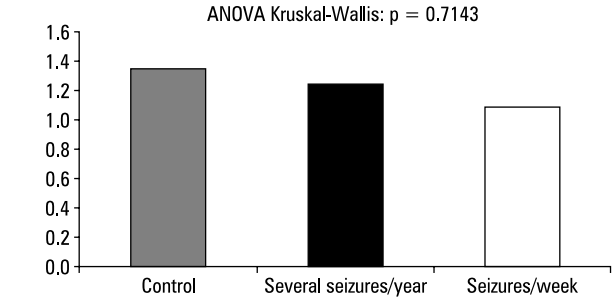
study performed by us, we showed that in patients with epilepsy, disturbances of circadian rhythm of ACTH concentrations were present. It is known that ACTH has an anticonvulsive action [15–17, 25]. However, we do not know if the excessive ACTH secretion observed in the patients studied by us takes part in the calming of seizures, or if it is only an effect of chronic stress response without such an action. ACTH shows anticonvulsive action also in the absence of adrenal tissue [14]. Immunocytochemical studies have shown large concentrations of ACTH-binding receptor in the hippocampus [26]. In Gallagher's studies [27, 28], patients with temporal epilepsy had increased ACTH concentrations in blood independently of frequency of seizures and their treatment. ACTH is an agent with demonstrated efficacy in the control of infantile spasms [14–16]. In West syndrome, pulsatile corticoid therapy was an effective alternative treatment to ACTH whereas in Lennox-Gastaut syndrome general steroids did not lead to a significant seizure reduction. In electrical status epilepticus during slow-wave sleep, treatment with pulsatile corticoid therapy seems to be effective [16]. The evaluation of the endocrine setup in epilepsy is difficult because of the coexistence of pharmacological interferences with hormonal function. A decrease in mean amounts of ACTH in blood was shown in patients with epilepsy treated with valproic acid [29], of cortisol in patients receiving phenytoin [30], and a slight increase of ACTH concentrations in the blood of patients using amizepin [29]. In Isojarvi's [31] study, cortisol concentrations in the blood of epileptic patients were not affected by therapy with carbamazepine. Conversely, DHEAS concentrations, which were decreased after two months of carbamazepine treatment, remained reduced in patients with long-term carbamazepine therapy, which is probably a result of accelerating DHEAS metabolism in the liver by enzyme induction. In another study, men with epilepsy had significantly lower DHEAS in blood [32, 33].

In our study we observed that an increase in the concentration of "big" endogenous opioids in blood (β-endorphin) was noticed in patients with severe (that is advanced in time or also in intensity) epilepsy and liberation of "small" endogenous opioid (leu-enkephalin) to blood was connected with the primary period of the disease. The pituitary gland and adrenal glands, the brain, and the digestive tract are, above all, the places

Table IX. *Mean daily concentrations of leu-enkephalin in the blood of patients with epilepsy in relation to frequency of seizure occurrence (groups with seizure occurrence — several per week and several per year) and in the control group*

Tabela IX. *Średnie dobowe stężenie leu-enkefaliny we krwi chorych na padaczkę w grupach wydzielonych w zależności od częstości napadów (kilka napadów na tydzień lub kilka napadów na rok) i w grupie kontrolnej*

Leu-enkephalin [pg/ml]	Group		
	Control	Several seizures/year	Seizures/ /week
Mean	1.34	1.24	1.09
SD	0.70	0.59	0.59
SEM	0.29	0.19	0.22
N	6	10	7

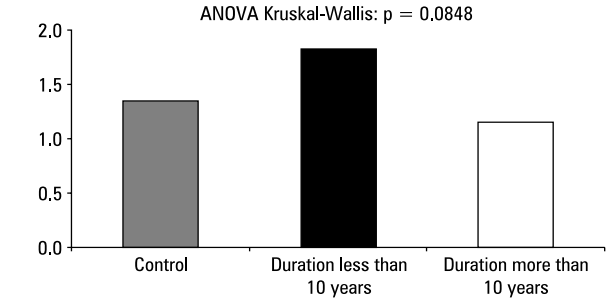


	Several seizures/year	Seizures/week
Control	p = 0.5876	p = 0.4751
Several seizures/year		p = 0.6256

Table X. *Mean daily concentrations of leu-enkephalin in the blood of patients with epilepsy in relation to duration of the disease (groups less than and more than 10 years) and in the control group*

Tabela X. *Średnie dobowe stężenie leu-enkefaliny we krwi chorych na padaczkę w grupach wydzielonych w zależności od czasu trwania choroby (mniej niż 10 lat lub ponad 10 lat) i w grupie kontrolnej*

Leu-enkephalin [pg/ml]	Group		
	Control	Duration less than 10 years	Duration more than 10 years
Mean	1.34	1.83	1.15
SD	0.70	0.57	0.50
SEM	0.29	0.21	0.14
N	6	7	10



	Duration less than 10 years	Duration more than 10 years
Control	p = 0.3176	p = 0.4537
Duration less than 10 years		**p = 0.0225**

of synthesis and secretion of endogenous opioid (leu-enkephalin). Taking into consideration the fact that hypophysectomy, not adrenalectomy, increases convulsion duration and abolishes progressive reductions in convulsion severity, it seems that this endogenous opioid produced in the central nervous system might be involved in the postictal refractory mechanism [34]. The changes of opioid peptide reactivity in seizure activity have been studied mainly in animals. It has been proven that β-endorphin shows anticonvulsive action if it is liberated in small amounts. In conditions of maintained seizural activity when it is liberated in larger amounts, it can participate in the development of status epilepticus [35]. The observed increase of leu-enkephalin content (but not β-endorphin and met-enkephalin) in cerebrospinal fluid was not caused by taking antiepileptic drugs or by structural pathological changes of the brain that might be found on CT scanning, but was a manifestation of neurohormonal disorders of the brain that resulted in epilepsy [1]. In another study, an increase in leu-enkephalin, and to a smaller degree in met-enkephalin-like immunoreactivity in the hippocampi of adults with generalized epilepsy, was noted. The hippocampi of six cadavers with a history of long-standing grand mal seizures were submitted for analysis [5]. It was shown that kappa-opioids in the hippocampus counteract initiation and maintenance of status epilepticus [2, 12], while delta-opioids promote initiation but not maintenance of seizure activity [12]. It was also shown that temporal lobe epilepsy is associated with alterations in mu-opioid and nociceptin receptor binding and signal transduction mechanisms downstream of these receptors [36]. The study of Zhang and Ko [37] provides supporting evidence of seizure activity involved in the up-regulation of brain-derived neurotrophic factor mRNA expression by activation of central mu-opioid receptors. The anterior cingulate cortex, which plays a role in pain, emotions, and behaviour, can generate epileptic seizures. This structure presents a high density of opioid receptors. Mu-opioid receptors appear to modulate both excitatory and inhibitory mechanisms, thus influencing epileptiform synchronization in this brain region [38]. Transcriptionally less active prodynorphin promoter alleles are associated with temporal lobe epilepsy, which might modify the risk of development of this epilepsy in subjects with a familial pre-

disposition [7]. An increase in the met-enkephalin levels in the striatum, cortex, pons, and medulla (but not in the hippocampi) in the genetically epileptic (tg/tg) mouse model of generalized epilepsy was noted [39]. Studies performed in rats showed an increase in enkephalin gene expression due to increased neuronal activity in the form of recurrent seizures [40], yet proenkephalin mRNA expression was increased after seizures in specific brain regions [41, 42]. Met-enkephalin mRNA was significantly increased in the hippocampus in rats after seizures. Phenobarbital abolished the seizures and the changes in neuropeptide expression [43]. Valproic acid induced rapid changes in met-enkephalin levels in the brains of rats with experimentally-caused epilepsy. This effect was also region specific. An increase in this peptide was observed in the striatum, a decrease in the midbrain, and no changes in the amygdala. These results suggest that striatal met-enkephalin may participate in the mechanism of the valproic acid-induced anticonvulsant effect [44]. It seems that the pharmacotherapy used additionally in epilepsy, by its influence on the endogenous opioid system, protects against liberating seizures and alleviates its clinical course [6].

Conclusions

1. Pituitary-adrenal axis hyperactivity is observed in patients with clinically active epilepsy independently of the frequency of seizures and duration of the disease.
2. Changes in endogenous opioid system activity are related to the clinical activity of epilepsy — β-endorphin plasma concentrations are connected with frequency of seizures and duration of the disease, and leu-enkephalin concentrations with duration of the disease.
3. Endogenous opioid peptides might take part in the neurochemical mechanism of human epilepsy.

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