Abstract:
In recent years, the functional disturbances of the immune system, both humoral and cell-mediated immunity, have been detected more often among persons with epilepsy than in general population. A number of irregularities in cytokine production have been found in epileptic patients. It shows that epileptic seizures stimulate, per se, synthesis of pro-inflammatory and pro-convulsive cytokines. Some antiepileptic drugs (AEDs) influence the production of cytokines, too. The influence of AEDs on cytokine concentrations in blood has been observed, e.g. during carbamazepine (CBZ) or valproic acid (VPA) therapy. This article is a review of the literature which focuses on the connections between epilepsy and the cytokine system as well as on the influence of AEDs on the cell-mediated and humoral response in epileptic patients. Correlation of immunological irregularities in patients with the type, dosage, and serum level of AEDs will allow for early detection of undesirable treatment consequences in epilepsy. Elucidation of connections between cytokine system, epileptogenesis and effectiveness of AED therapy requires a better planned research on larger groups of patients with epilepsy.

Key words:
epilepsy, cytokines, antiepileptic drugs, interleukins

Abbreviations:

Introduction
The epilepsy is the disease occurring in about 1–2% of the population [71]. Its etiology is varied. There are groups of patients with symptomatic epilepsy whose
organic changes originate from the central nervous system (CNS) injury during pregnancy and in the perinatal period. Some epilepsies can originate from inflammatory changes or traumatic events in early childhood, ion channel malfunction as well as metabolic or degenerative diseases [14, 34, 40, 60]. Genetically determined decrease in convulsive threshold occurs in the families predisposed to the epileptic seizures, dependent on specific endo- or/and exogenous stimuli. Epileptic seizures occur due to genetically determined disturbances of receptors in the CNS and neurotransmitters or metabolic disorders. In about 2/3 cases, we cannot identify the factors which are responsible for seizure occurrence [40]. Undoubtedly, genetic and environmental factors facilitate the contact of brain antigens with the immune system. It is known that cytokines constitute the link between those two important systems in the human body [1, 6, 8, 14, 16, 27, 34, 58, 69]. It is a well-known fact that lymphocytes have receptors for neurotransmitters, whereas receptors for numerous cytokines are present on neurons and glia [6, 8, 22, 27]. Dysregulation and excessive production of the whole spectrum of cytokines can lead to degeneration of neurons, caused by neurotoxic influence on them, and can induce seizures [16, 32, 35, 49, 58]. In recent years, the functional disturbance of the immune system, both humoral and cell-mediated immunity, has been detected more often among persons with the epilepsy than in the general population [1, 15, 18, 27, 43]. The onset of different types of epilepsy occurs above all in developmental age and the disease riches the peak of morbidity in early childhood and in pubescence. In this case, AED treatment begins and is continued in adolescence, e.g. at the time of forming different organs, systems and immunologic connection with the CNS

Cytokines – types, function and connection with the CNS

Cytokines are a group of proteins which are extensively used for inter-cell communication. They are a diverse class of compounds in terms of origin and function. They are significant for the appropriate functioning of both innate and adaptive immune response. Apart from their importance to the development and functioning of the immune system, cytokines play a major role in a variety of immunological, inflammatory and infectious diseases of the CNS, as well [15, 16, 27, 29, 45]. Various mediators of inflammation are present in the brain, cerebrospinal fluid (CSF) and blood in epileptic patients [6, 45]. The histological analysis of human brain from individuals with epilepsy of various etiologies strongly suggests the existence of a chronic inflammatory process in the brain. It is associated with neuronal loss, reactive gliosis or malformations of cortical architecture. Such chronic inflammation in the brain may be implicated in the etiopathogenesis of seizures and the associated long-term consequences [15, 16, 27, 29, 45, 49, 62, 65]. Not until recently did scientists believe that the CNS was the immunologically privileged place. It turned out that major histocompatibility complex type I particles (MHC I) were essential in the ontogenic function during the so-called “new generation” AED therapy [1, 3]. It is not widely known that AEDs cause a dysfunction of the immune system or escalate the disturbances which had appeared earlier. Probably, there is a grain of truth in both hypotheses [1, 3, 11, 36, 45, 72]. Genetic and environmental factors facilitate the contact of cerebral antigens with the immune system and induce inflammatory reaction. This facilitates production of specific antibodies reacting with antigens located on nerve cells and neuroglia, which disrupts their homeostasis [15]. That reaction may induce cascade of cytokine production which may be followed by convulsions [15, 25, 27, 35, 49]. Certainly, the correlation between immunological irregularities in patients and different types, doses and serum levels of the AEDs can allow for early detection of side effects of AED treatment, too. The immune system disturbances connected or not with AEDs can be one of the reasons why the applied therapy fails.
development of the brain i.e. in formation of neuronal connections in the visual cortex [22]. Moreover, it was observed that antigens of the cerebral origin were able to enter and induce the immunological response in peripheral lymph glands, despite the lack of lymphatic vessels in the CNS [57, 72]. Cytokines are also involved in several developmental processes during embryogenesis. Cytokines and chemokines regulate neurotrophins and other molecules critical to neurodevelopmental processes and the exposure to certain neuroimmune challenges early in life affects brain development. In adults, cytokines affect synaptic plasticity and other ongoing neural processes, which may change in aging brains [29, 58]. Inflammation plays a role in epileptogenesis and in the progression of the disease [15, 20, 45, 62, 65]. Untouched blood-brain barrier (BBB) is not a hindrance to the activated lymphocytes T although some cytokines, e.g. interleukin (IL)-6, IL-2, tumor necrosis factor-α (TNF-α) can increase considerably its permeability [5, 22]. Inflammatory mediators are also produced by brain parenchymal cells (microglia, astrocytes and neurons), by cells of the BBB and choroid plexus. Cytokines can enter the brain by the passive and/or active transport, e.g. TNF-α, IL-6 [5, 6, 32, 62, 65]. Endothelial cells of blood vessels play an important role in the mechanism of this barrier’s permeability. Direct influence of cytokines on endothelial cells of cerebral vessels has been observed. Furthermore, the induction of various mediators, e.g. nitric oxide (NO) or prostaglandins (PGs) has been detected. Besides, the peripheral concentration of cytokines is important because it can influence the transcription of genes regulating cytokine expression in the CNS. Microglia is the only population of cells which permanently express MHC II molecules on their surface [72]. Due to the expression of the MHC II, astrocytes and pericytes can present antigens on their surface [57, 72]. This process is intensified by interferon gamma (INF-γ) produced by lymphocytes T. Astrocytes, microglial cells and lymphocytes T, which are present in the CNS, can produce and secrete the whole spectrum of cytokines [69]. They intensify the immunological response by chemotactic influence on macrophages and other effector cells [15, 29, 57]. They play an important role in the disturbances of tissue homeostasis [15, 16, 27, 58]. Cytokines are produced by a wide variety of cell types and by neurons and glia, as well [49]. The cytokine family consists mainly of smaller water-soluble proteins and glycoproteins with molecular weight of 8–30 kDa [19, 28, 51]. They bind to a specific cell-surface receptor. Subsequent intracellular signaling cascades alter cell functions. Those proteins may cause the up-regulation and/or down-regulation of several genes and their transcription factors. This situation leads to the production of other cytokines, an increase in the number of surface receptors for other molecules, or the suppression of their own effect by feedback inhibition. A lot of cytokines have similar functions. They are characterized by pleiotropism. Different cells may express receptors for more than one cytokine, or many different tissues can express receptors for the same cytokine [15, 19, 28, 51, 58]. Generalization of cytokine functions is not possible, because one interleukin can act on the cell that secretes it, its effect may be restricted to the immediate vicinity of a cytokine secreting cell or it can diffuse to distant regions of the body to affect different tissues [58]. The term interleukin is used by researchers for those cytokines whose presumed targets are principally leukocytes [19, 28, 51]. Cytokines have been divided into four types. The first one contains four α-helix bundle family which is divided into three subfamilies (IL-2, INF, IL-10). The second one includes IL-1 family, the next one comprises IL-17 whereas chemokines belong to the last group. A clinical classification divides immunological cytokines into those that promote the proliferation and functioning of type-1 helper T-cells (T\textsubscript{H1} cells), e.g. INF-γ and those which stimulate type-2 helper T-cells (T\textsubscript{H2} cells), e.g. IL-4, IL-10, IL-13, transforming growth factor β (TGF-β) [19, 28, 51]. The cytokine receptors are equally important as cytokines, because their deficiency can be directly linked to certain debilitating immunodeficiency states. A classification of cytokine receptors is based on their three-dimensional structure and distinguishes several receptor families, viz. immunoglobulin superfamily, e.g. IL-1 receptor, growth factor family, e.g. IL-2 receptor, interferon family, e.g. INF-β and INF-γ receptor, TNF family, e.g. TNF-β receptor, seven transmembrane helix family, e.g. ubiquitous receptor, G-protein coupled receptor for hormones and neurotransmitters [19, 28, 29, 51]. There is an extensive bidirectional communication between the nervous and the immune system in both health and disease. Immune cells and neuroimmune molecules, such as cytokines, chemokines, and growth factors modulate brain function through multiple signaling pathways throughout the lifespan. Immunological, physiological and psychological stres-
sors engage cytokines and other immune molecules as mediators of interactions with neuroendocrine, neuropeptide and neurotransmitter systems [6, 15, 16, 27, 58, 62, 63, 65].

Actually, IL-1 is a whole family of cytokines which belong to the most important regulators of the immunological and inflammatory response. First of all, IL-1 is not only secreted by macrophages and monocytes, but also by glial cells and vascular endothelial cells in the CNS [49]. The most studied molecular forms of IL-1 are: IL-1α and IL-1β which bind to the same receptor. The IL-1 receptor agonist IL-1Ra is an agent which binds to the same receptor on the cell surface as IL-1, and thus prevents IL-1 from sending a signal to that cell [21, 23]. Among many IL-1 functions, there is its influence on the permeability of vascular endothelium. This cytokine intensifies adhesion of lymphocytes and neutrophiles to these cells, which facilitates their penetration to tissues, also in the CNS [49]. IL-1β stimulates neovasculogenesis. Inter alia, IL-1β can induce the synthesis of nerve growth factor (NGF), ciliary neurotrophic factor (CNTF) and insulin-like growth factor (IGF) from astrocytes and it stimulates antioxidant pathways that can promote repair processes in the CNS [6, 23, 62, 65]. IL-1β resets the hypothalamus thermoregulatory center, leading to an increased body temperature. IL-1β can induce fever by stimulating the production of PGs in the hypothalamus and fever of any cause induces IL-1β in brain microglia [23, 49, 62, 65]. The IL-1 may cause the excessive sleepiness and anorexia. It also influences adrenocorticotropic hormone (ACTH) and corticotropin releasing hormone (CRH) secretion [6, 15, 16, 21, 23]. IL-1β acts pro-convulsively through escalation of the glutamatergic transmission [17]. This cytokine inhibits uptake of glutamates by astrocytes and lowers gamma-aminobutyric acid (GABA) quantity in the hippocampus [62–66]. IL-1β inhibits glutamate reuptake by astrocytes and increases glutamate release by these cells [27]. That cytokine can inhibit GABAergic transmission [17, 62, 65]. Frequently, abnormalities in plasma levels of this cytokine are observed in children with complex febrile convulsions. Also a risk of temporal lobe epilepsy is significantly higher than in this population [13, 23, 24, 31]. Spontaneous paroxysmal activity and sensitivity threshold to proconvulsant factors depends on alleles of IL-1β gene. Complex febrile convulsions appear significantly more often in homozygotes bearing IL-1B−31C/−511T allele [13, 31]. This cytokine plays a functional role in the chronic changes in neurotransmission induced in brain tissue by an acute epileptic event [49]. Convulsant and/or excitotoxic stimuli increase the production of IL-1β in microglia-like cells in the hippocampus. IL-1β enhances focal electrographic seizures induced by kainate through an increase in glutamatergic neurotransmission [32, 42, 48, 50, 52]. Increased production of IL-1 has been shown in human temporal lobe epilepsy thus suggesting that this cytokine may play a role in the neuropathology of the epileptic tissue [64]. Different genetic programs regulate the inflammatory response. So homozygosity for allelic variants of the IL-1β gene promotes enhanced cytokine production. The analysis of IL-1β, IL-1α, and IL-1Ra gene polymorphisms in drug-resistant epileptic patients may suggest an association between cytokine gene haplotypes and development of focal seizures [23, 62, 65].

IL-2 is a glycosylated protein which, like IL-1, takes part in inflammatory response, especially in microbial infections. IL-2 mediates its effects by binding to IL-2 receptors, which are expressed by T lymphocytes [22]. Bacterial antigens, via receptors on T cells (TCR), stimulate the secretion of IL-2 and simultaneously the expression of IL-2 receptors (IL-2R) on these cells [8]. The IL-2/IL-2R interaction causes the growth, differentiation and survival of antigen-select- ed T cells via the activation of the expression of specific genes. IL-2 is also necessary for development of T cell immunologic memory and maturation of regulatory T cells (T-Regs) [7, 59]. IL-2 is secreted by lymphocytes T. This cytokine influences proliferation, activation and differentiation of lymphocytes T, lymphocytes B and natural killer (NK) cells [8, 27, 43]. IL-2 exerts an analgesic effect by influencing opioid receptors in the brain [21, 22]. Other IL-2 functions include protection of neurons and regulation of neurotransmitters and hormones in the CNS. IL-2 takes part in the modulation of bioelectric activity of the brain [7, 22]. IL-2 modifies activity of dopaminergic neurons and, therefore, this cytokine has an indirect influence on serotonergic, cholinergic, noradrenergic, glutamatergic neurotransmission [7, 27, 59]. This interleukin has a significant influence on sleep and memory processes. Receptors for this interleukin are found in several parts of the brain, e.g. in the frontal lobes, hippocampus, hypothalamus, cerebellum and in pituitary gland [22].

IL-4 stimulates the proliferation of activated B cells and T cells, but also differentiation of CD4+ T cells into Th2 cells. This cytokine induces B cells to
class switching and IgE production. It causes up-regulation of MHC class II. IL-4 is one of the most important regulators in humoral and adaptive immunity [21]. Liu et al. noticed that non-neoplastic astrocytes expressed IL-4Rα and responded to IL-4 [37].

IL-6, like IL-1, is one of the fundamental cytokines which regulates the immunological response of the organism. It is not only produced by macrophages and monocytes, but also by vascular endothelial cells [3, 21]. IL-6 is a pro-inflammatory cytokine secreted by T cells and macrophages to stimulate immune response to trauma, especially burns or other tissue damage leading to inflammation [15, 27, 45]. Its too high blood concentration may accelerate osteoporosis. IL-6 is one of the most important mediators of fever and of the acute phase response [8, 45–47, 62, 63, 65]. IL-6 also stimulates pituitary gland to secrete CRH [21]. In the muscle and fatty tissue, IL-6 stimulates energy mobilization which leads to increased body temperature. IL-6 can be secreted by macrophages in response to pathogen associated molecular patterns (PAMPs) binding to the Toll-like receptor (TLR) present on an active macrophage. IL-6 signals are transmitted through a cell-surface receptor complex by its signal-transducing component gp130 (CD130) [21, 35, 70]. Signal transduction cascade initiates Janus kinases (JAKs), and signal transducers and activators of transcription (STATs). Also other cytokines use this receptor to transduce signals, e.g. IL-11, CNTF or oncostatin M (OSM). These cytokines are commonly referred to as the IL-6-like or gp130-utilizing cytokines. In addition to the membrane-bound receptor, a soluble form of IL-6R (sIL-6R) has been purified from human serum and urine [35]. Many neuronal cells are unresponsive to stimulation by IL-6 alone, but differentiation and survival of neuronal cells can be mediated through the action of sIL-6R. The sIL-6R/IL-6 complex can stimulate neurite outgrowth, promote survival of neurons, hence, it may be important in nerve regeneration through remyelization [21, 35]. The statistically significant increase in the IL-6 concentration in serum and CSF has been found after the tonic-clonic seizures with simultaneous increase in the acute phase protein concentration (peak about 6 hours) [45–47, 62, 63, 65]. IL-6 causes the increase in sensitivity to glutamatergic agonists [62, 63, 65]. Simultaneously, decreasing concentrations of soluble components of interleukin receptor (sIL6R and sGp130) have been observed. The rise of the IL-6 concentration is more evident after tonic-clonic seizures, occurring mainly in clusters rather than after a single, partial seizure [45]. It shows that epileptic seizures stimulate synthesis of cytokines [35, 45, 66, 67].

IL-10 is known as human cytokine synthesis inhibitory factor (CSIF). IL-10 is one of the anti-inflammatory proteins, capable of inhibiting synthesis of pro-inflammatory agents, like: INF-γ, IL-2, IL-3, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), by macrophages and TH2 cells [41]. It is mainly expressed in monocytes and TH2 cells, mast cells, and also in a certain subset of activated T cells and B cells. IL-10 reduces also the expression of MHC class II molecules and certain co-stimulators, e.g. B7, can have stimulatory actions on B cells and may function as a switching factor for the production of IgG4 in humans. It inhibits monocyte-induced production of IFN-γ by NK cells. Moreover, it indirectly causes this inhibition by suppressing monocyte production of IL-12 [12, 21, 41].

IL-12 is involved in the differentiation of naïve T cells into TH1 cells, which is important in resistance to pathogens. It is known as a T cell stimulating factor, which can stimulate the growth and function of T cells. It stimulates the production of INF-γ and TNF-α from T and NK cells and also reduces IL-4-mediated suppression of INF-γ. T cells, which produce IL-12, have a co-receptor (CD30) which is associated with IL-12 activity. IL-2 stimulates the expression of two IL-12 receptors, β1 and β2, maintaining the expression of a critical protein involved in IL-12 signaling in NK cells. IL-12 has also antiangiogenic activity through inducible protein 10 (IP-10) [12, 21, 68].

TNF belongs to cytokines which stimulate acute phase reaction. TNF is a whole family of particles produced chiefly by monocytes, lymphocytes and macrophages [3, 5, 21]. TNF-α is released from leucocytes, endothelium and different damaged tissues after stimulation by e.g. IL-1, bacterial endotoxin [3]. TNF stimulates secretion CRH, it may suppress the appetite, causes fever and increases production of C-reactive protein (CRP) [6, 33, 55]. TNF stimulates macrophages to phagocytosis and production of IL-1, oxidants, inflammatory lipid, PGE2. It also facilitates the adhesion of lymphocytes to the endothelial cells what enables transmigration [27]. Receptors for cytokines are located on almost all nuclear cells of our organism [21]. TNF leads to the increase in resistance of different tissues to insulin. It escalates local symptoms of inflammation: heat, swelling, redness and pain [33, 55]. TNF-β has cytoprotective activity and
activates repair processes, but also stimulates the ability for phagocytosis and potential cytotoxicity [5]. Activated microglia can produce cytokines, e.g. IL-1, IL-6 [3]. In pathological conditions, high cytokine concentrations, especially INF-γ, cause expression of MHC II on the majority of cells in the CNS [21]. Balosso et al. noticed that recombinant TNF-α, which was given to the mouse hippocampus, might cause inhibition of abnormal paroxysmal activity [5]. It has been observed that epileptic seizures in transgenic mice with higher expression of TNF-α receptor gene on astrocytes were rarer and lasted shorter than in normal population of mice [5].

Cytokines in epilepsy

Some abnormalities in production of cytokines have been observed in epileptic patients. Interleukins are released by immunocompetent cells after the stimulation by different endo- and exogenous stimuli, which can disturb neuronal homeostasis [1]. This process may induce abnormal paroxysmal activity and may cause disturbances in complicated neurotransmitter systems, which leads to clinical seizures [6, 22, 32, 49, 58, 60]. The high level of IL-1R α (natural antagonist of IL-1β) located on astrocytes has been found about 18–24 hours after the seizure [49]. Receptors for anti-inflammatory IL-4 have been found on astrocytes [37, 62, 65–67]. In patients with the drug-resistant epilepsy, the increase in the serum pro-inflammatory cytokine concentrations, particularly, the increase in IL-6 concentration, and decrease in the IL-1R a level and the IL-1R α/IL-1β ratio have been confirmed [47]. The higher titer and activity of pro-inflammatory cytokines are found in CSF [1, 2]. It proves that the above-mentioned cytokines are synthesized by glial cells in the CNS [25, 49, 62, 65–67]. Pro-inflammatory cytokines can activate the hypothalamic-pituitary-adrenal axis and influence sympathetic nervous system [16]. The stress-induced release of hypothalamic CRH consequently leads to the systemic secretion of glucocorticoids (GCs), which influences the immune and inflammatory reactions. Conversely, immune molecules, in particular IL-1, IL-6, and TNF-α stimulate CRH secretion [6, 16, 22, 29, 62, 65].

It is known that TNF-α and IL-1 may modify synthesis of neurotransmitters, and that interleukins have influence on ion currents through neuronal membrane [13, 27]. It is a well-known fact that hippocampal damage induces production of pro-inflammatory cytokines, like IL-1 and TNF-α [49]. Equally important is the expression of their receptors in different parts of the brain [23, 27]. A number of irregularities in cytokine production has been found in persons with epilepsy. Microglia and astrocytes are the first cells which produce cytokines during seizures [69]. They represent the main sources of pro-inflammatory molecules in the brain [1]. Cytokines are soluble mediators that can establish functional communication between microglia, astrocytes and neurons [16, 63].

Recent evidence has shown that inflammatory cytokines and their receptors are present in various forebrain areas, and both neurons and glia are local sources of their synthesis. IL-1β induces synthesis of IL-6, TNF-α by astrocytes and microglia [66]. The effect of inflammatory cytokines not only depends on the functional state of neurons, but also on concentration of cytokines and the duration of tissue exposure to them. IL-1Ra is an endogenous protein, which, by binding with IL-1, can inhibit seizures [49]. So, changes in the IL-1/IL-1Ra ratio are natural mechanism to control seizures [23, 66].

The temporal lobe epilepsy (TLE) is characterized by focal seizures arising from either the neocortex or the mesial temporal structures [30]. An increased IL-1α expression in microglia-like cells has been documented by immunohistochemistry in brain specimens obtained from patients surgically treated for TLE [4, 9, 30]. IL-1β, TNF-α and IL-6 are expressed at very low levels in normal brain, but protein levels are rapidly increased after the induction of seizures, declining to basal levels within 2–3 days after seizures. Pro-inflammatory cytokines are also induced in the brain by audiogenic and kindled seizures [23, 52, 53, 62, 65]. Up-regulation of IL-1 receptor antagonist, a natural antagonist of IL-1β, has been described after acute seizures, status epilepticus, and in kindling [49, 52]. Cytokine receptors in the CNS are expressed by neurons, microglia and astrocytes [62, 65]. IL-1β acts in the CNS through the IL-1 type 1 receptor: IL-1β activates the p38 mitogen-activated protein kinase (MAPK) pathway in neurons, leading to the induction of cyclic adenosine monophosphate (cAMP) response element–binding protein, whereas nuclear factor kappa B (NF-κB) is activated predominantly in astro-
cytes, suggesting that this cytokine may have distinct functional effects on neurons and glia [38, 58]. IL-1 and TNF-α receptors are rapidly unregulated in neurons during seizures [29, 39, 53, 62, 65]. Statistically important increase in IL-6 plasma levels after a cluster of tonic-clonic seizures was noticed [45, 47]. It seems to be possible that epileptic seizures activate production of pro-inflammatory and proconvulsive cytokines, e.g. IL-6, IL-1β, TNF-α. IL-6 receptor and its signaling transducer protein, Gp130, are increased in rat forebrain and in the meninges after seizures [13, 35, 45, 62, 65]. The effect of TNF-α on seizures depends on its endogenous brain levels and the receptor subtypes predominantly stimulated by this cytokine [62, 65]. Various pro-inflammatory cytokines studied in experimental models of acute seizures either decrease the threshold for seizure induction or increase the duration and severity of epileptiform activity. Fibroblast growth factor (FGF), TNF-α and IL-1Ra inhibit seizures and afford neuroprotection, depending on their concentration, their short- or long-term increase in the brain. IL-1β, IL-6, and TNF-α modulate ionic currents both in neurons and in glia [13, 47, 49, 53].

A direct interaction between TNF-α and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors has been noticed in hippocampal neurons. This cytokine, via p55 receptors, stimulates AMPA receptors and amplifies the glutamate responses [17]. In experimental research on animals, the increased production and secretion of pro-inflammatory cytokines, e.g. IL-6, IL-1β and TNF-α in the hippocampus shortly after tonic-clonic seizures was proven. In status epilepticus, expression of the above-mentioned interleukins is significantly higher [32, 45, 47]. There are more and more indications that cytokines are involved in determining neural excitability. IL-1β and TNF-α increase in the whole brain tissue after the rats were kindled by electrical stimulation of the amygdala [20]. A pronounced up-regulation of mRNAs of various cytokines, such as IL-1β, IL-1R a, TNF-α, have been observed in the parietal, piriform and prefrontal cortices, hippocampus in the amygdala-kindled rats [52]. The obtained data clearly showed a net increase in the level of TNF-α both in the cortex and cerebellum of kindled animals [20, 52]. Limbic seizures in rodents provoked by intraperitoneal administration of kainite and it results in recurrent seizures [48]. This is a useful model of temporal lobe epilepsy [32, 42]. Kainate-induced seizures lead to neuronal loss mainly in the hippocampus [32, 42, 48, 50, 52]. Status epilepticus induced by this substance causes activation and proliferation of astrocytes and microglia in regions of damaged neuronal tissue [42]. Cytokines produced by glia, lymphocytes and macrophages regulate the process of neuronal reorganization. Synthesis of IL-1β, IL-6, IL-1Ra and NO have been noticed in stimulated hippocampus. High doses of exogenous IL-2 can promote seizure generation in various models of experimental epilepsy. Increased concentrations of pro-inflammatory cytokines during infection may cause neurological dysfunction leading to seizures [10]. However, increasing IL-10 protects tissues against pro-inflammatory action of other cytokines [1, 2, 32, 41]. Researches on animals revealed an increasing production and secretion of pro-inflammatory cytokines (IL-6, IL-1β, TNF-α) in the hippocampus, shortly after tonic-clonic seizures. Experimental models of seizures revealed some interesting conclusions. Epileptic activity per se is sufficient not only to induce a prominent inflammatory response in the brain, but also seizure-induced inflammation [1, 10, 45, 60]. Inflammation is more extensive when seizures are associated with cell damage [62, 65]. From a clinical standpoint, the role of inflammation in the pathophysiology of human epilepsy is still hypothetical, although this possibility is supported by abundant evidence [10, 62, 65].

### Epilepsy, cytokines and AEDs

Patients with drug resistant epilepsy have higher serum levels of aforementioned cytokines than persons with well-controlled seizures. Researches revealed that some AEDs had an important influence on cytokine production [11, 56]. The increased IL-2 level was noticed during CBZ therapy, but changes in the levels of IL-2, IL-6, and TNF-α in patients treated by VPA were not so unambiguous. Some AEDs have influence on the production of interleukins, especially when they are used in polytherapy [11]. The rise in the IL-2 concentration has been proven during the CBZ therapy [11, 43]. Influence of AEDs on the blood cytokine concentrations has been observed, e.g. the increase in secretion of IL-1α, IL-1β, IL-6, IL-2 during the CBZ therapy and decrease in IL-2, IL-6,
TNF-α concentrations during VPA therapy [43, 54, 61]. Doubtlessly, VPA has an influence on the immune system [26, 56]. Shah et al. conducted research on ten healthy volunteers who were treated with VPA. On the seventh day of therapy, all of them had significantly higher serum level of IL-6 [54]. Verrotti et al. noticed that the production of IL-1α, IL-1β, IL-6, IL-2 was not so significant during VPA therapy as in patients receiving CBZ [61]. However, Ichiyama et al. revealed that the production of cytokines, e.g. TNF-α and IL-6 by monocytes and glia was decreased under the influence of VPA [10, 26, 67]. Probably, it is caused by inhibition of activity of the NF-κB, which is necessary to correct the expression of those cytokines [26, 38, 39, 71]. Due to the incompatibility of reports on the influence of VPA on cytokine system, that problem needs more investigations [56]. Recent tonic-clonic seizures in epileptic patients induce a pro-inflammatory profile of cytokines in plasma and CSF, consisting of higher IL-6 levels and lower IL-1α-to-IL-1α ratio [45, 47]. Because CSF IL-6 concentration is much higher than that measured in plasma and the contribution of peripheral blood mononuclear cells (PBMCs) to increased plasma levels of cytokines is still unclear, the brain appears to be the most likely origin of CSF cytokines [25]. An increased expression of pro-inflammatory molecules has been demonstrated in neurons and glia in brain tissue obtained from patients surgically treated for drug resistant epilepsies [4, 25, 62, 65]. Changes in the production of cytokines in the patients treated by “new” AEDs have not been described in the available literature so far. Establishing a correlation of immunological irregularities in patients with the type, the dose and with level of the AEDs in the blood serum will allow for early detection of undesirable treatment consequences of epilepsy. The disturbances in the expression of multidrug transport proteins may not only cause AED resistance, but also facilitate the entry, e.g. immunoglobulins to the CNS [25, 62, 65].

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