The Pathogenesis of Epilepsy

Subjects: Others

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Epilepsy is a chronic neurological disorder characterized by recurring spontaneous seizures. Drug resistance appears in 30% of patients and it can lead to premature death, brain damage or a reduced quality of life. The purpose of the study was to analyze the drug resistance mechanisms, especially neuroinflammation, in the epileptogenesis. The information bases of biomedical literature Scopus, PubMed, Google Scholar and SciVerse were used. To obtain full-text documents, electronic resources of PubMed Central and Research Gate were used. The article examines the recent research of the mechanisms of drug resistance in epilepsy and discusses the hypotheses of drug resistance development (genetic, epigenetic, target hypothesis, etc.). Drug-resistant epilepsy is associated with neuroinflammatory, autoimmune and neurodegenerative processes. Neuroinflammation causes immune, pathophysiological, biochemical and psychological consequences. Focal or systemic unregulated inflammatory processes lead to the formation of aberrant neural connections and hyperexcitable neural networks. Inflammatory mediators affect the endothelium of cerebral vessels, destroy contacts between endothelial cells and induce abnormal angiogenesis (the formation of “leaky” vessels), thereby affecting the blood–brain barrier permeability. Thus, the analysis of pro-inflammatory and other components of epileptogenesis can contribute to the further development of the therapeutic treatment of drug-resistant epilepsy.

drug-resistant epilepsy epileptogenesis neuroinflammation

1. Introduction

Neuroinflammation is mediated by the synthesis of cytokines, chemokines, reactive oxygen species and secondary messengers. These mediators are produced by the central nervous system (CNS) resident glia (microglia and astrocytes), endothelial cells and peripheral immune cells. Neuroinflammatory reactions lead to immune, physiological, biochemical and psychological consequences. The purpose of the study was to analyze the drug resistance mechanisms, especially neuroinflammation, in epileptogenesis, as well as the currently available hypotheses of the drug resistance of epilepsy. Neuroinflammation aspects vary depending on the disease, trauma, exposure to toxic substances, infection or stress experienced [1]. Diseases with an autoimmune component such as optic neuromyelitis and multiple sclerosis [2], aging and obesity [3] can also be considered triggers of inflammation. Accumulating evidence suggests that neuroinflammation plays an important role in the etiology of mental disorders, a variety of neurological and somatic diseases, including epilepsy, Alzheimer’s disease, Parkinson’s disease, autism spectrum disorders, bipolar disorder, affective disorders, depression [4][5][6][7][8] and systemic lupus erythematosus [9][10]. Recent data suggests that neuroinflammation is one of the key processes in glaucoma and retinopathy [11][12][13][14], it is also important in the pathogenesis of heart failure [15]. Frequent or chronic inflammation can also have dangerous consequences, contributing to the development of malignant

neoplasms [16] or to the metastasis of cells of existing tumors to the brain [17]. Recent immunological studies in psychiatry have led to the hypothesis of mild encephalitis (ME) in the pathogenesis of severe mental disorders. The ME hypothesis assumes the course of mild neuroinflammation, which is rather difficult to detect using available diagnostic methods [18]. The definition of autoantibodies targeting synaptic and neuronal cell surface proteins (NMDAR, AMPAR, GABAßR, etc.) in ME reflects its autoimmune nature, which has helped diagnose psychiatric autoimmune encephalitis. The presence of these autoantibodies was manifested mainly by psychiatric symptoms (psychosis), while neuroinflammation was proven in brain biopsies, and the so-called subtle epilepsy was also diagnosed using electroencephalography (EEG) [19]. Immunomodulatory therapy reduces the incidence of psychosis in autoimmune encephalitis [20]. Thus, neuroinflammation is an integral feature of many neurological disorders. Neuroinflammation does not mean a poor prognosis and some aspects of the neuroinflammatory response may be useful for restoring the CNS, for example, in the axon regeneration and their remyelination in the cases of multiple sclerosis, traumatic spinal cord injury, stroke and Alzheimer's disease. Conclusions that neuroinflammation may be beneficial should not be surprising [21].

2. Materials and Methods

In preparing the review, the main and most famous information bases of biomedical literature, Scopus (766), PubMed (1419), Google Scholar (17 300) and SciVerse (192), were used. To obtain full-text documents, electronic resources of PubMed Central (PMC) and Research Gate were used. The text of the review cites 87 contemporary publications for 2014–2021, reflecting the latest discoveries, as well as 2 publications for 2008 and 2009. The search was carried out for the following words and phrases: drug-resistant epilepsy, refractory epilepsy, epileptogenesis, neuroinflammation. The topic of the selected articles was as close as possible to the topic of this article. Preference was given to articles in English with high citation, published in journals with a high impact factor in 2019–2021. The selection of sources included both individual independent studies and review articles with open access which examined the nature and manifestations of drug-resistant epilepsy in animals and humans, since the data for humans and experimental animals may differ, which offers evidence for the hypotheses considered. For selected articles, the number of published articles by the author in the given research area, the total number of citations of the author's publications, the total number of publications cited by the author and the Hirsch index were estimated.

3. Epilepsy, the Characteristics of the Pathogenesis, the Relationship with Inflammatory Processes. Drug-Resistant Epilepsy

Epilepsy is a chronic neurological disease characterized by recurrent spontaneous seizures. Epilepsy affects approximately 1.0% of the world's population [22]. The prevalence and frequency of epilepsy is slightly higher in men compared to women. The general prognosis of epilepsy is favorable for the majority of patients and 55–68% of them tend to achieve long-term remission [23], but in the case of generalized tonic-clonic seizures, nocturnal seizures and refractory or drug-resistant epilepsy, death is not uncommon [24]. The development of epilepsy can be

associated with a wide variety of factors, including genetic predisposition, malformations, traumatic brain injuries that occur annually in 64–74 million people [25], chemical exposure, hypoxia or stroke. Many of these pathologies are associated with neuronal death. In 1971, M. Taylor discovered a disorder of the neocortex organization in patients operated on for drug-resistant epilepsy. Later, this disorder was called focal cortical Taylor dysplasia. Histologically, with Taylor's dysplasia, there is an increase in the number of the cerebral cortex layers or their thickness, the presence of giant and dysmorphic neurons, "balloon cells" and heterotopy of neurons in the subcortical white matter [26]. Focal cortical dysplasia can be detected in almost half of patients with drug-resistant epilepsy [27]. Brain damage triggers a cascade of biological events characterized by neuroinflammatory processes —the release of cytokines, chemokines, lipid mediators and proteins in the neuronal microenvironment. In the brain, such mediators activate microglia and astrocytes, alter cerebrovascular function, affect the infiltration of peripheral inflammatory cells, promote cell proliferation or apoptosis and alter ion transport, neurotransmission and communication between neurons [28].

Currently, the role of complement in the pathogenesis of epilepsy has been shown. Complement activation can be caused by necrotic cells, cellular fragments or a misfolded protein such as the fibrillar form of amyloid β-peptide in Alzheimer's disease [29]. Activated microglial and astrocyte cells synergize with other pro-inflammatory cascades, thus accelerating pathogenesis and neuronal dysfunction [30]. The complement includes about 30 plasma and cell membrane proteins that interact with each other, triggering a series of inflammatory responses involved in protecting against infection [31]. Dysregulation of the classical (C1inh, C4), alternative (FH, properdin, C3) and terminal (TC) pathways also contributes to the pathogenesis of epilepsy [31]. Overexpression of various complement proteins has been demonstrated in surgically removed tissue of patients with epilepsy, as well as in rodent models [32][33].

Cytokines are mainly produced by microglia and astrocytes in the CNS. They play a role in its development and normal functioning, as well as in numerous inflammatory reactions in neurodegenerative diseases [31][34][35]. Some regulation mechanisms of cytokine secretion and their receptors expression have been described in patients with epilepsy [36]. For example, increased concentrations of serum IL-1b, IL-1Ra, IL-2, IL-4, IL-6, IL-8, IFNy and IL-17 have been observed in patients with epilepsy [37][38], as well as increased levels of IL-6 and IL-17 in the cerebrospinal fluid [39]. Several researchers have shown that the concentration of IL-4, IL-8 and IL-17 can correlate with the frequency and severity of seizures, suggesting a key role for cytokines in the diagnosis and treatment of epilepsy [38][40]. Most chemokines and their receptors promote neuroinflammation by involving peripheral monocytes and promoting glial cell activation [25]. Table 1 provides examples of some mediators involved in neuroinflammation and epilepsy and their role in these processes.

Table 1. Some mediators involved in neuroinflammation and epilepsy.

Complement System	
C3, C4, Properdin, FH, C1Inh and Clu	Known as markers of epilepsy [32][33]. Components including C9, C8, C4-B are activated in patients. Consequently, the complement cascade is involved in the chronic epileptic phase in animals and humans. Complement activation can promote a sustained inflammatory

Complement System	
	response and destabilize neural networks involved in the pathological process [32]. In epilepsy, both classical (C1inh, C4) and alternative (FH, properdin, C3) pathways are damaged. These proteins allow to distinguish patients with well-controlled epilepsy from uncontrolled ones [31][32].
C3	Genetic polymorphisms in the promoter region obtained in patients suggest C3 role in the genetic predisposition to febrile seizures and epilepsy [31][32]. C3 deficient mice were found to be more resistant to seizures [32]. Serum C3 level is elevated in untreated patients compared to control and treated patients [32].
C1q and iC3b	The elevated levels of these proteins are registered in brain tissue samples from patients with drug-resistant epilepsy. C1q has been implicated in the pathological elimination of synapses in the context of schizophrenia and dementia. Elevated C1q and iC3b levels have been reported in human brain samples with focal cortical dysplasia. Thus, it can be assumed that aberrant complement activation occurs in patients with drug-resistant seizures [31][32].
Membrane Attack Complex (MAC)	MAC is recorded in activated microglia and neurons in the brain tissue of patients and animals with epilepsy. Sequential intrahippocampal injection of individual MAC proteins induces convulsions and neurodegeneration in rats [32].
Cytokines	
IL-1β	Elevated level of IL-1β suggests that inflammation is involved in the pathophysiology of epilepsy. In the CNS, IL-1β is mainly produced by activated microglia but also by neurons, astrocytes and oligodendrocytes. In a healthy brain, IL-1β is present at a low level, participating in the processes of sleep, learning, memorization and neuromodulation. In chronic and acute inflammatory processes in CNS, it plays both a useful and harmful role. IL-1β levels in the peripheral blood of patients may reflect the severity of seizures. It can inhibit gamma-aminobutyric acid (GABA)-mediated neurotransmission, inhibit glutamate uptake by astrocytes and modulate neuronal arousal. Inhibition by an IL-1RI antagonist or prevention of synthesis has a neuroprotective effect [41].
IL-2, IL-8, IL-18	In patients and animal models of epilepsy, increased expression levels of these cytokines in the brain are observed. They increase the excitability of neurons and thus are considered to be involved in epileptogenesis [25][41].
Arg1, IL-4 and IL-10	There is an increase of anti-inflammatory cytokines expression (Arg1, IL-4 and IL-10) by microglia in epilepsy [25]. IL-10 is usually characterized as an anti-inflammatory cytokine. In combination with transforming growth factor beta (TGF-ß), it inhibits a number of pro-inflammatory mediators, such as IL-1α, IL-1β, IL-6, IL-8, IL-12, IL-18, TNF-α and granulocytes, thus modulating glial activation. The anticonvulsant effect of IL-10 has been confirmed by studies in animal models [41].
IL-6	IL-6 is expressed by a number of brain cells, including astrocytes, microglia and neurons. IL-6 plays a controversial role in neuroinflammation, it can act as a pro-inflammatory cytokine, increasing the chemokine secretion and adhesion molecules, or inhibit TNF-α, reduce neurotoxicity, promoting differentiation and survival of neurons. IL-6 overexpression in CNS leads to aberrant hippocampal arousal, spontaneous seizures and neurodegeneration [25][41].

Complement System	
TNF-α	TNF-α probably plays a dual role as a pro- and anti-inflammatory cytokine, depending on the time, size, cell targets and signaling cascades involved, being both pro- and antiseizure [41].
TGF-β	Signaling of TGF-β has been shown to trigger seizures, neuronal hyperexcitability and epileptogenesis. Transcriptome analysis also confirms the role of TGF-ß signaling in epileptogenesis. Astrocytic transmission of TGF-ß signals induces excitatory synaptogenesis, which precedes the development of seizures [25].
NLRP3	The expression of the main component of inflammasomes (NLRP3) increases in the cerebral cortex of patients with refractory epilepsy. NLRP3 activates caspase-1, which leads to the processing of proinflammatory cytokines IL-1β and IL-18 [42].
Chemokines	
Fractalkin (FKN, CX3CL1)	This transmembrane chemokine is expressed by neurons of CNS. Several studies have shown its role in the epilepsy pathogenesis and concomitant cell death. Blocking of CX3CL1/CX3CR1 signaling pathway by antibodies reduces microglial activation and neurodegeneration caused by an electrical epileptic seizure in rodents [43].
CCL2	CCL2 expression is increased in the epileptic brain of humans and animals. Suppression of this chemokine can inhibit brain damage caused by seizures [41][44].
CCR7, CCR8, CCR9, CCR10	Production of these chemokines is suppressed in the hippocampus in animal models of epilepsy, the consequences of this suppression are not established yet [41].
CCL5, CCL19, CCL22, CXCL8	Elevated levels of these chemokines are observed in patients with epilepsy, traumatic brain injuries and in animal models of epilepsy [41].
Chemokine Receptor 7 (CXCR7)	CXCR7 is involved in the epilepsy pathogenesis and mediates the immune response in the brain. CXCR7 inhibition in the hippocampus had an antiepileptic effect on mice [45].

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therapeutic regimens with one or more drugs [47]. The only thing that remains unchanged is that it is possible to detect drug resistance in clinical practice only after unsuccessful courses of treatment with several ASMs. At the primary diagnosis, it is very difficult to predict whether and how high the risk of developing such epilepsy is, excepting of certain diseases, such as West's syndrome or Lennox–Gastaut syndrome. A poor prognosis is more likely to be expected in people with mental retardation and serious deviations from the norm on the electroencephalogram [48].

Neurosurgical resection of the epileptic focus [49] or neurostimulation [50][51] can help such patients. These methods reduce the seizure frequency by 10–80%. It is considered promising to switch to a ketogenic diet, for example, the modified Atkins diet [52], which has been used since 2003 to treat children and adults with refractory epilepsy at Johns Hopkins Hospital in Maryland, USA [53]. Other dietary regimens, such as calorie restriction and a gluten-free diet, can also have a positive effect [54]. In the absence of an effect, drugs based on cannabidiol or its synthetic analogues can be prescribed as palliative care, reducing the number of epileptic seizures in about 80% of patients but the frequency of side effects is high—from 42 to 71.4% [55][56]. Drug resistance is not an absolute category. Six trials involving 2411 people aged 16 to 80 years showed that treatment with the third-generation ASMs

Brivaracetam, a high-affinity ligand for the synaptic vesicle protein 2A, showed a decrease in seizure frequency by 50% and more, compared with placebo groups [57]. Most seizures, even in the case of drug-resistant epilepsy, stop spontaneously. In particularly severe cases of so-called “super-refractory epilepsy”, when the seizure lasts 24 h or more and there is a risk of irreversible damage to neurons and their death, almost all experts use “aggressive” therapy with continuous intravenous infusions of midazolam, pentobarbital or propofol in the intensive care hospital department. In this case, the seizure can be stopped almost always but the overall mortality rate can reach 48%. About one fifth of patients with refractory epilepsy are at risk of this [58].

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