PROSPECTS OF FINDING PATHOLOGICALLY BASED THERAPIES FOR EPILEPSY ASSOCIATED WITH BRAIN GLIOMA

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In recent decades, scientific research on tumor-associated epilepsy has increasingly focused on the study of the biochemical and molecular mechanisms of the brain tumor and peritumoral tissues, opening up new and unprecedented perspectives in understanding the glioma-associated epilepsy pathogenesis and treatment. Evidence suggests that neurons play a central role in tumor growth and cancer cells, in turn, can reconfigure the nervous system and its functions. Extracellular glutamate levels in the tissue around the glioma are up to 100 times higher than those in the healthy brain, as detected. At the same time, the available data support the idea that the excitatory neurotransmitter glutamate is the most significant mediator of the seizures related to glioma. The article reports some aspects of the cerebral glioma pathogenesis. The authors believe that modern antiepileptic drugs can affect the neoplastic process course. A number of antiepileptic drugs having the antitumor potential are presented.

Keywords: tumor-associated epilepsy, glioma, primary brain tumors, neurooncology, antiepileptic drugs

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ПЕРСПЕКТИВЫ ПОИСКА ПАТОГЕНЕТИЧЕСКИ ОБОСНОВАННОЙ ТЕРАПИИ ЭПИЛЕПСИИ, АССОЦИИРОВАННОЙ С ГЛИОМОЙ ГОЛОВНОГО МОЗГА

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В последние десятилетия научные исследования глиальных опухолей головного мозга в большей степени сосредоточены на изучении биохимических и молекулярных механизмов как в самой опухолевой, так и в перитуморальной ткани, что открывает новые и беспрецедентные перспективы в понимании патогенеза и терапии эпилепсии, ассоциированной с глиомами. Данные свидетельствуют о том, что нейроны играют центральную роль в росте опухоли и, в свою очередь, раковые клетки могут изменять конфигурацию нервной системы и ее функций. В ткани, окружающей глиому, выявляются уровни внеклеточного глутамата до 100 раз выше, чем в здоровом мозге. В то же время существующие данные подтверждают концепцию о том, что возбуждающий нейромедиатор глутамат является важнейшим медиатором припадков, связанных с глиомой. В статье описаны некоторые аспекты патогенеза глиомы головного мозга. По мнению авторов, современные противоэпилептические препараты могут влиять на течение опухолевого процесса. Представлен ряд противоэпилептических препаратов, имеющих противоопухолевый потенциал.

Ключевые слова: опухоль-ассоциированная эпилепсия, глиома, первичные опухоли головного мозга, нейроонкология, противоэпилептические препараты

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According to the 2017 ILAE Classification of the Epilepsies, the brain tumor-associated epilepsy is a structural focal epilepsy that is diagnosed in 10-15% of epilepsy cases. Back in 1947, in the fifth edition of Diseases of the Nervous System, John Eastman Wilson mentioned that generalized seizures may be the first symptom of an intracranial tumor, noting the fact of a later onset of tumor-associated epilepsy in contrast to idiopathic epilepsy. In 2003, K. Luiken and his colleagues from the University of Bonn proposed calling this group "long-term epilepsy-associated tumors" (LEATs) [1]. The group includes glioneuronal tumors and some astrocytomas, more often of low malignancy.

The most common tumors of the central nervous system are glioblastomas (grade IV gliomas according to the WHO classification). The average age of disease onset is 64 years, and the overall five-year survival rate is 6.8% — one of the worst across the entire range of cancers. With low-grade gliomas, 70-90% of patients suffer from epileptic seizures when the tumor is detected, whereas with glioblastoma, seizures are less common (up to 60%) [2].

Pathogenetic processes underlying the development of gliomas and tumor-associated epilepsy

According to recent data, neurons play a central role in tumor growth, and pathological cells, in turn, can change the configuration of the nervous system and its functions. There

is evidence of the formation of functional synapses between neurons and glioma cells [3].

Epileptogenesis in peritumoral tissue is a multifactorial process. Glioblastomas and tumor-associated epilepsies have common pathophysiological mechanisms that underpin both tumor progression and the persistence of epileptic seizures. One of the main pathological vehicles is the aberrant transmission of glutamate signals in the tumor tissue and its microenvironment. The levels of extracellular glutamate registered in the tissue surrounding the glioma were found to be up to 100 times higher than those peculiar to the healthy brain. On the one hand, a high level of glutamate stimulates the proliferation and invasion of glioma cells, and on the other hand, it can lead to epileptic seizures, excitotoxicity and, consequently, boost the volume of the tumor and the area it occupies [4].

In the past decade, the cystine/glutamate antiporter (SLC7A11, or xCT) has been recognized as an important factor in various processes of tumor progression: it is the main transporter of cystine into the cell, exchanging it for glutamate, which subsequently promotes the synthesis of glutathione needed to protect cells from oxidative stress. [5].

Another mechanism that increases the amount of glutamate is expression of the BCAT1 gene, which encodes the cytosolic form of the branched chain amino acid transaminase enzyme. The level of BCAT1 expression is an important prognostic factor for glioma patients, since it is associated with the malignant progression of wild-type IDH1 gliomas [6]. Thus, BCAT1 is a promising target for the treatment of primary glioblastoma and gliomas.

There is evidence that a growing amount of glutamate in peritumoral tissue increases the risk of tumor necrosis; it is an important prognostic factor supporting an unfavorable outcome. The excitatory effect of glutamate is realized through the activation of three main types of ionotropic receptors and several classes of metabotropic receptors associated with G proteins. Ionotropic receptors are those interacting with N-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA), and kainic acid (KA) [7]. The permeability of AMPA receptors to Ca^{2+} is determined by the presence or absence of the GluR2 subunit in the receptor complex.

The analysis of the drug resistance of glioblastomas also revealed epigenetic modifications, in particular DNA methylation, which determines the progression of the tumor. MicroRNAs, a non-coding class of RNA, play a significant role in this process. MicroRNAs with both pro-oncogenic and protective effects were identified, as well as epigenetic modifications of microRNAs that can alter their expression in glioblastoma through methylation. Clarifying the form of epilepsy by examining specific microRNAs in blood plasma, especially in clinically complex cases, can help select the most effective antiepileptic therapy [8].

Thus, it is obvious that there are common mechanisms of pathogenesis of peritumoral changes and generation of epileptic seizures, and the described processes become cascading, mutually reinforcing and accelerating each other. Disrupting or slowing down the pathological processes will not only solve the problem of epileptic seizures but also allow controlling the growth of the tumor.

Search for antiepileptic drugs with potential antitumor effects

Currently, it can be said that drugs that alter the mechanisms behind an epileptic seizure can highly likely affect tumor aggression, too. Thus, timely antiepileptic therapy improves the survival of glioblastoma patients. In light of the hypothesis that glutamate released from glioma cells can not only activate surrounding neurons (causing epileptic seizures and triggering excitotoxicity processes) but also boost the progression of glioma, the preferred drugs for patients with partial and generalized seizures should be those with antiglutamate action [9].

Perampanel used for epilepsy in patients with IDH1-wild type and MGMT-unmethylated glioblastoma stopped seizures and supported survival for 18 months [10].

An in-depth and comprehensive review of various aspects of epileptogenesis in cerebral glioblastoma cases gives basis for the selection of drugs. While there have not been developed specific recommendations addressing the choice of an anticonvulsant for tumor-associated epilepsy, the identification of compounds with antitumor effect *in vitro* is a persistent subject of interest. Numerous preclinical studies have shown that levetiracetam can enhance the glioblastoma response to temozolomide [11]. Brivaracetam, with its molecule similar in structure to that of levetiracetam, should produce the same effect. Moreover, brivaracetam's action can be more pronounced, since this drug is better tolerated than levetiracetam.

From our point of view, brivaracetam and lacosamide, the latest antiepileptic medicines, show promise in treatment of tumor-associated epilepsy. The authors hypothesized that they hinder the release of glutamate not only from neurons but also from astroglia [12]. Lacosamide inhibits histone deacetylase, suggesting an antitumor effect that requires further investigation. Indeed, the respective mechanism has been considered as blocking the cell cycle in glioma cells, possibly by activating miR-195-5p microRNA. The researchers have also suggested that by modulating other microRNA modifications (miR-107), lacosamide can inhibit cell growth, enhance apoptosis, and block cell migration and invasion. A great advantage of this drug is the possibility to administer is parenterally in equivalent doses.

Currently, one of the most promising combinations of antiepileptic drugs in cases of epilepsy associated with cerebral gliomas may be that of levetiracetam and lacosamide. It can effectively control epileptic seizures and mixes well with adjuvant radiochemotherapy, which mitigates the risk of adverse events stemming from the treatment of the underlying disease. However, the encouraging results from in vitro studies that looked into the effect of levetiracetam and lacosamide on glioblastoma were not fully confirmed in in vivo studies, which yielded mixed results regarding patient survival [13].

CONCLUSION

The analysis of literature shows that the problem of the pathogenesis of tumor-associated epilepsy is a matter of interest for many researchers. The related modern concepts revolve around both biochemical disorders in the peritumoral zone as a result of blastomatous growth, and the kindling effect associated with impaired neural migration [14]. However, there is a number of specific issues related to the diagnosis and therapy of the disease that have not been studied sufficiently. The problems of early diagnosis of primary brain tumors remain relevant. The subjects requiring attention in the first place are clinical diagnosing, the study of the semiology of the attack, which allow formulating indications, designing a neuroimaging techniques application algorithm, and suggesting histology and classification of the degree of tumor anaplasia. Currently, neuroimaging algorithms are becoming more complex in parallel with the development of technology [15]. There is no single strategy for choosing antiepileptic drugs against a tumor-associated epilepsy. Meanwhile, clarifying the mechanisms of

epileptogenesis is a prerequisite both for the development of therapeutically effective antiepileptic drugs and for improving strategies for the comprehensive treatment of tumor-associated epilepsy. Excessive activity of glutamate and its receptors boosts the growth of glioma itself and promotes apoptosis and epileptic activity in the peritumoral region. The foci of epilepsy activity and glioma can affect each other. There is probably a pathological vicious circle in which tumor growth provokes epileptic seizures, and excessive neural activity can stimulate tumor progression. The combination of antiepileptic drugs with different mechanisms of action will improve the prognosis and the quality of life of patients with brain tumor-associated epilepsy [16]. Perampanel, a selective, non-competitive AMPA antagonist, may be one of the drugs of choice for additional therapy of the related epileptic seizures [16]. Other new antiepileptic drugs, such as lacosamide and brivaracetam, can probably affect both the quality of life of patients and their survival (given in pathogenetically justified combinations). The use of antiepileptic drugs that induce microsomal liver enzymes of the P450 system should be avoided, since sch action may reduce the effectiveness of chemotherapy. In addition, the use of inhibitors of the P450 system may increase the risk of adverse events caused by chemotherapeutic drugs. Clarification of the patterns of epileptogenesis is required both for the development of effective anticonvulsants and for the improvement of strategies designed for complex treatment of tumors associated with epilepsy.

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