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Etiopathogenetic mechanisms of epilepsy and comparative characteristics of audiogenic epilepsy experimental models

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SUMMARY

Epilepsy is a widespread neurological chronic disease characterized by recurrent seizures, manifested as short-term partial or generalized convulsions and accompanied by loss of consciousness. To correctly select a treatment method for epilepsy, it is necessary to investigate the cues resulting in its development, but it is not always possible to identify a cause of the disease and chose proper treatment. Drug resistance remains one of the major issues in treatment of epilepsy, despite a great body of studies describing its nature. In this regard, it is necessary to select a model for examining epileptic seizures and underlying mechanisms, searching for genes involved in regulation of epilepsy as well as assessing effectiveness and safety of new antiepileptic drugs. It was noted that rodents, especially Krushinsky–Molodkina rat strain represent a suitable genetic model for audiogenic epilepsy to dissect the mechanisms of epileptogenesis, genetic basis of seizure susceptibility, development of drug resistance, and testing new antiepileptic drugs. Despite that the audiogenic form of reflex epilepsy is quite rare in humans, it was revealed that the same underlying genes, molecular mechanisms and signaling pathways are responsible for enabling audiogenic seizures in rodents and human epilepsy, additionally coupled to developing similar neuroanatomical anomalies.

KEYWORDS

Epilepsy, audiogenic seizures, models of epilepsy, Krushinsky–Molodkina rats.

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Этиопатогенетические механизмы эпилепсии и сравнительная характеристика экспериментальных моделей аудиогенной эпилепсии

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РЕЗЮМЕ

Эпилепсия – распространенное неврологическое хроническое заболевание, для которого характерны повторяющиеся припадки, проявляющиеся в виде кратковременных парциальных или генерализованных судорог и сопровождающиеся потерей сознания. Для правильного подбора способа лечения эпилепсии необходимо исследовать факторы, вызывающие ее развитие, однако не всегда удается выявить причину заболевания и подобрать адекватное лечение. Лекарственная устойчивость остается одной из главных проблем при лечении эпилепсии, несмотря на большое количество работ, описывающих ее природу. В связи с этим следует подобрать модель для изучения эпилептических припадков и их механизмов, поиска генов, участвующих в регуляции эпилепсии, а также оценки эффективности и безопасности новых противоэпилептических препаратов. Отмечено, что грызуны, в особенности крысы Крушинского–Молодкиной, являются подходящей генетической моделью аудиогенной эпилепсии для изучения механизмов эпилептогенеза, генетических основ предрасположенности к судорожным состояниям, развития лекарственной устойчивости и тестирования новых противоэпилептических лекарств. Несмотря на то что аудиогенная форма рефлекторной эпилепсии достаточно редко встречается у человека, выявлено, что в реализации аудиогенных припадков грызунов и эпилепсии человека участвуют одни и те же гены, молекулярные механизмы и сигнальные пути, возникают сходные нейроанатомические аномалии.

КЛЮЧЕВЫЕ СЛОВА

Эпилепсия, аудиогенные припадки, модели эпилепсии, крысы Крушинского–Молодкиной.

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INTRODUCTION / ВВЕДЕНИЕ

It is known that any brain has a tendency to seizures, which occur when the excitability of an area or areas exceeds a certain threshold. Epilepsy is a group of heterogeneous neurological conditions in which one or many factors of different nature lead to a decrease in the internal convulsive threshold, which increases the tendency to spontaneous recurrent seizures [1]. It is a chronic neurological disease characterized by recurrent spontaneous seizures. Approximately 0.5–1.0% of the world's population suffers from it [2].

The prevalence and frequency of epilepsy is slightly higher in men compared to women and, as a rule, reaches

a peak in old age, along with other diseases of the nervous system: neurodegenerative, strokes and malignant tumors. The general prognosis of epilepsy is favorable for most patients and 55–68% of them tend to achieve long-term remission [3], but in the case of generalized tonic-clonic seizures, nocturnal seizures and so-called refractory or drug-resistant epilepsy, death is not uncommon [4].

The development of epilepsy can be associated with a variety of factors, including genetic predisposition, developmental dysfunction, traumatic brain injuries that more than 64–74 million people receive annually [5], chemical exposure, hypoxia or stroke. In almost 30% of cases, it is not possible to find out the cause, and, consequently, to choose an adequate treatment.

There are several hypotheses about the nature of drug resistance (including pharmacokinetic, transport, neural network hypothesis, internal complexity, genetic and epigenetic, target hypothesis and hypothesis that puts neuroinflammation and apoptosis in the first place), but none of them is able to explain the causes of drug resistance. Most likely, in the case of each individual patient, resistance is mediated by several mechanisms, the contribution of which may vary, including over time. Despite the emergence of various new antiepileptic drugs with different mechanisms of action, drug resistance remains one of the main problems in the treatment of epilepsy [6].

Apoptosis of neurons and brain glial cells is of great importance in the pathogenesis of epilepsy, especially drug-resistant forms. Frequent and prolonged seizures lead to brain damage, but even short single seizures can induce the development of apoptosis of neurons and glia. Aberrant neuronal death is one of the main causes of chronic neurodegenerative diseases [7, 8].

CLASSIFICATION AND CAUSES OF EPILEPSY / КЛАССИФИКАЦИЯ И ПРИЧИНЫ ЭПИЛЕПСИИ

Classification / Классификация

The first international classification of epilepsy and epileptic syndromes was adopted in 1989 and subsequently revised by the International League Against Epilepsy (ILAE). Currently, epilepsy is classified according to the revised terminology and concepts for the organization of seizures and epilepsies [9, 10]. The new classification does not represent a fundamental change in understanding the nature of epilepsy but provides greater flexibility and transparency for diagnosis [11]. According to this multilevel classification, each case of epilepsy in humans is considered from several sides: the type of seizure, localization (focal, generalized, combined focal-generalized, and unclassified), characteristics of the epileptic syndrome and its etiology (**Fig. 1**). The starting point here is the type of attack, which can have a focal, generalized or unknown onset. Many forms of epilepsy include several types at the same time; there is a group of combined generalized and focal epilepsies. In the case of unspecified epilepsy, the diagnosis is difficult to make due to insufficient available data, such as the absence or errors of electroencephalography.

According to the types of seizures, they are divided into atonic with loss of consciousness and rapid recovery, clonic (irregular short-term seizures characterized by rapid periodic contraction and relaxation of muscles), tonic with prolonged muscle tension, myoclonic with rapid contractions of various muscle groups, and non-convulsive, in which a person simply loses consciousness [11]. According to the localization and degree of brain structures involvement, focal, generalized, combined and unspecified forms of epilepsy are distinguished (see Fig. 1).

The set of characteristics includes the type of seizure, electroencephalography readings, other neuroimaging techniques, as well as signs of comorbidity.

Causes / Причины

According to the current classification, the causes of epilepsy are divided into six categories: structural, genetic, infectious, metabolic, immune and remaining unexplained. However, in a given patient, epilepsy may have more than one cause [10, 12].

Structural epilepsy is characterized by congenital or acquired damage to certain brain structures: strokes, injuries, developmental abnormalities. Theoretically, any structural damage to the brain can lead to seizures and epilepsy. The most common and often surgically removed injuries include hippocampal sclerosis, tumors, malformations of the cortex and its feeding vessels, glial scars after injuries and strokes, areas affected by inflammation.

The genetic causes of epilepsy are various mutations. Classical epidemiological studies have shown that about a quarter of epilepsy cases are based on an acquired cause – injuries, strokes, infections and other diseases. In the remaining 75% of cases, it is not possible to find it, and in many of them genes are the cause. In addition, the role of genetic factors may be significant, even if the cause of epilepsy is clear [13].

The development of next-generation sequencing techniques makes it possible to identify more and more genes that contribute to the etiology of epilepsy, including very rare variants. At the same time, only a small part of epilepsies refers to monogenic diseases, and the majority is based on the incorrect operation of many genes. Each individual mutation may not pose a particular danger, but together they lead to the development of epilepsy. Identifying mutations is crucial because some of them are potentially curable. In the case of some genetically determined epilepsies, for example, sodium channels pathologies, the risk of a patient's sudden death is high.

Metabolic causes partially overlap with them, that is metabolic disorders, often hereditary. Acquired metabolic

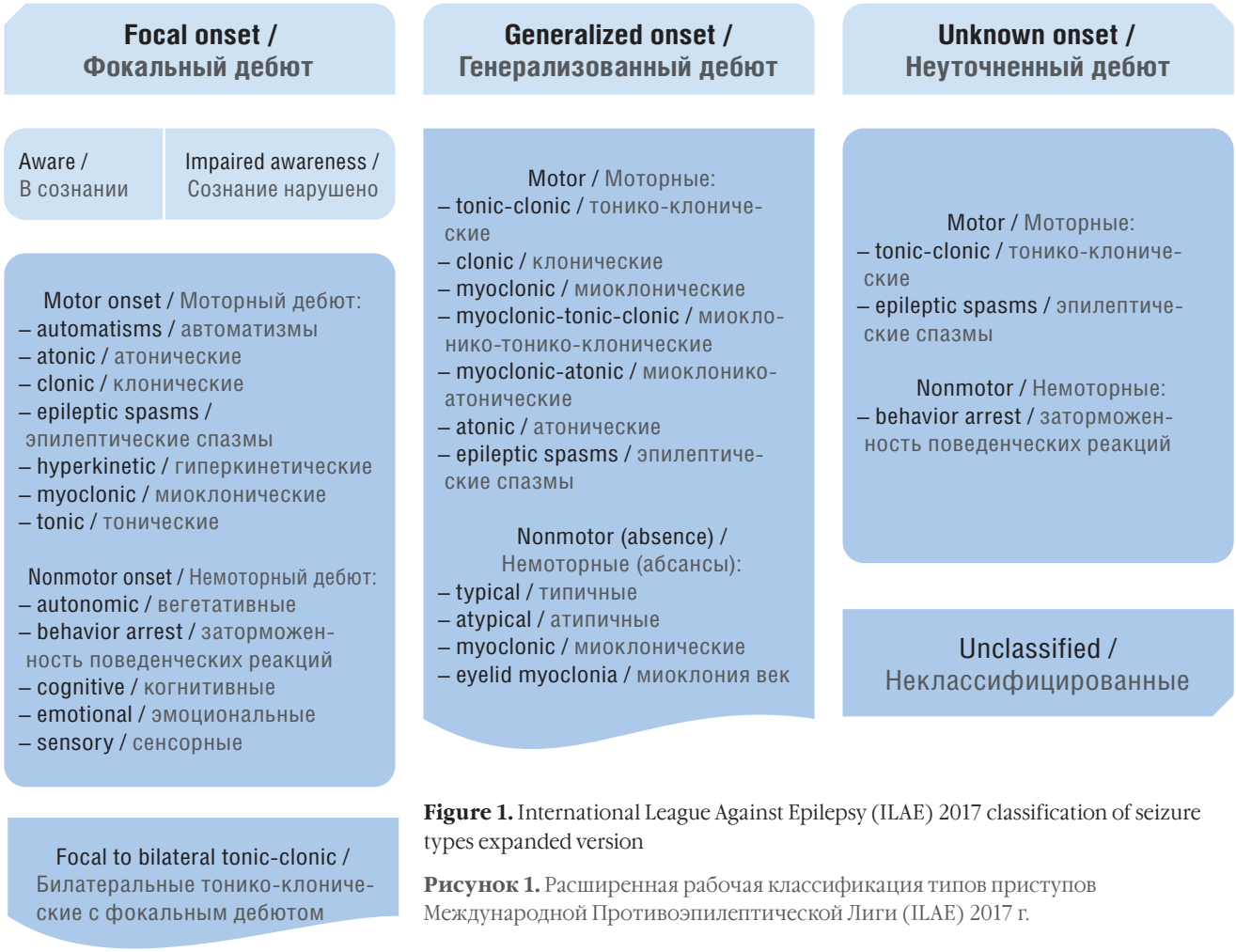

Figure 1. International League Against Epilepsy (ILAE) 2017 classification of seizure types expanded version

Рисунок 1. Расширенная рабочая классификация типов приступов Международной Противоэпилептической Лиги (ILAE) 2017 г.

disorders may occur due to renal or hepatic insufficiency, diabetes mellitus, nutritional deficiencies, poisoning with toxicants or medications. Many of these lead to seizures, but not to epilepsy. Congenital metabolic disorders are infrequent among the causes of epilepsy, although more than 200 genetic, including mitochondrial, metabolic disorders associated with epilepsy have been identified. They often respond poorly to treatment or add to the number of cases of refractory epilepsy. These include pyridoxine-dependent epilepsy with a mutation of the antiquitin gene (*ALDH7A1*) [14].

Infectious epilepsies develop as a consequence of transferred or chronic neuroinfections, including intrauterine ones. Any severe systemic infection that does not even affect the brain causes metabolic disorders and can trigger autoimmune processes. But it is cerebral infections caused by bacteria, viruses, fungi and parasites that are one of the most common causes of seizures and epilepsy worldwide, and especially in developing countries. Convulsions can repeatedly, 18 times in the case of bacterial meningitis, increase the lethality of an already deadly disease. In the poorest regions, such as sub-Saharan Africa, infections cause epilepsy in a quarter of patients [15].

Epilepsy can also be an autoimmune disease. Autoimmune processes rarely affect the brain, but a number of diseases such as systemic lupus erythematosus, sarcoidosis, celiac disease, Behcet's disease and Hashimoto's encephalopathy affect brain function. Currently, many antibodies associated with seizures are known, but the pathogenic significance of some autoantibodies specifically associated with seizures is still unclear. It has been proved that a significant part of epilepsy in patients with unclear etiology has an autoimmune cause [16].

For many people with epilepsy, the cause is unknown. In this category, it is not possible to make a specific diagnosis other than the basic electroclinical symptomatology, such as frontal lobe epilepsy. This etiology is not absolute, because diagnostic capabilities vary between medical institutions and countries [10].

All of these reasons may be combined or may never be discovered. Recently, neurodegenerative factors can be added to them [1, 9]. It is important to consider the presence of comorbidities in each patient with epilepsy at each stage of classification, which allows for early detection, diagnosis and appropriate treatment [10].

REFLEX EPILEPSY / РЕФЛЕКТОРНАЯ ЭПИЛЕПСИЯ

Every tenth person on the planet faces seizures. They can occur in a variety of cases and with different diseases. Not all convulsive states can be considered epilepsy, but epilepsy is any disorder in which spontaneous recurrence of unprovoked seizures is the main symptom [17].

Reflex seizures are epileptic phenomena that objectively and consistently occur in response to a certain afferent stimulus or activity of the patient. The variety of such stimuli is extremely large, from a flash of light, exercise, fright, eating, listening to music, watching TV, video games, reading a book, to complex internal ones. Epileptic seizures, which are clearly provoked by a specific perceptual stimulus, were first discovered in the 2nd century AD. Reflex epilepsy is classified as a specific syndrome in which all epileptic seizures are provoked by sensory stimuli. At the same time, in most patients, along with such seizures, spontaneous seizures, which are common for epilepsy, also occur.

The overall prevalence of reflex epilepsy is 4–7% in all patients with epilepsy and more than 21% in idiopathic generalized epilepsy. The most common stimuli in humans are visual, accounting for up to 75–80% of the total number of cases. It is important to note that seizures caused by drug withdrawal, fever, severe emotional distress, loss of sleep, etc. are not considered epilepsy [18].

Audiogenic and musicogenic epilepsy / Аудиогенная и музыкогенная эпилепсия

A special case of reflex epilepsy is audiogenic, which occurs in animals, including humans [19]. Classical audiogenic epilepsy, when seizures are caused by simple acoustic stimuli in humans, is practically not observed, and reflex auditory epilepsy, classified as idiopathic generalized, is caused by complex combinations of sounds, memories, emotional state, etc. [20].

This form of epilepsy is extremely rare, and its frequency is approximately 1:10000000 people with a predominance in women. The exact prevalence of audiogenic and musicogenic epilepsy is unknown, since patients often do not consider sound stimuli as a trigger, and in electroencephalography, sound is not used to provoke an attack. Descriptions of seizures caused by music appeared as early as 1841, and in 1937, musicogenic epilepsy was isolated into a separate form, but from 1884 to 2007, only 110 such cases were registered in the world [21].

Seizures are most often focal, with or without impaired consciousness, originate from the temporal lobes, with rare secondary generalization. It has been hypothesized that such epilepsy may be based on dysregulation of the hippocampus and prefrontal cortex, mediated by changes in dopaminergic signaling, stress and emotional dysregulation [18]. This condition has been known for more than 75 years but has not yet been fully investigated. In some cases, seizures can be triggered by the mere thought of a melody, and epileptiform activity can be prevented or stopped by listening to some other music. Triggers can also be other sounds, for example, the ringing of bells or the operation of mechanisms [22].

Musicogenic seizures differ from simple stimulatory audiogenic seizures by the complexity of the trigger and are probably related to the emotional aspect of music perception or memory. This type of epilepsy usually develops at a later age than the usual audiogenic [21].

AUDIOGENIC EPILEPSY IN ANIMALS / АУДИОГЕННАЯ ЭПИЛЕПСИЯ У ЖИВОТНЫХ

However, audiogenic epilepsy is not uncommon in animals for which hearing plays a much more important role, while their survival depends on the quality of hearing and rapid response to danger. Seizures develop in a similar pattern in animals of different species and genotypes. Model laboratory animals, both intact and genetically predisposed to seizures, are of great importance for studying the mechanisms of epileptogenesis, searching for genes and regulatory pathways associated with epilepsy, as well as testing new antiepileptic drugs. Among this diversity, it is the genetic models of audiogenic epilepsy that stand out.

Cats / Кошки

Audiogenic seizures have been noted in cats and have been called feline audiogenic reflex seizures (FARS). They are most often manifested in animals over the age of 15 years with concomitant diseases and are induced by high-frequency sounds lying in the range of about 40 kHz, such as rustling foil, ringing glass, phone call or alarm sound. In some cats, spontaneous myoclonic seizures are observed without an obvious noise stimulus.

The disease has a hereditary nature, as it is more common among Burmese cats. One of the mysteries of the syndrome is audiogenic seizures in deaf cats or with serious hearing disorders. Perhaps, in such animals, the cochlea region that perceives high frequencies was not affected, and they only seemed deaf to humans [24, 25].

Cats have not found a use as laboratory animals for the study of audiogenic epilepsy, since they have seizures at a late age, when animals have many concomitant diseases, and are not a stable syndrome. In addition, the age of the appearance of seizures (15 years) makes it inconvenient to use them as a model.

Chikens / Куры

Audiogenic as well as photogenic reflex epilepsy due to an autosomal recessive mutation affects chickens of the Fayoumi line (Fepi). All Fepi chickens have sound-induced seizures from hatching from the egg to adulthood. Their

seizure source is localized in the brain stem, which makes chickens a potentially good model for studying hereditary reflex epileptic syndromes of animals and humans [24].

Rodents / Грызуны

However, most studies are performed on rodents. In addition to the main advantages of rodents, such as simplicity of maintenance, undemanding food and fast reproduction rate, relatively short life span, morphophysiology close to humans, they are characterized by a stable nature of seizures, no need for invasive effects and the introduction of toxic chemical compounds, ease of visualization and good reproducibility of results [27].

Their epilepsy is undoubtedly hereditary. The first confirmation of this was the successful selection of rat lines with audiogenic epilepsy, followed by an increase in penetrance and frequency of seizures. Regardless of the type and line of rodents prone to convulsions in response to sound stimulation, they were found to have increased acoustic thresholds, such as thresholds of cochlear action potentials, and various morphological anomalies of the cochlea along with neurochemical abnormalities, dysfunction of ion channels, imbalances in GABAergic[1] nd glutamatergic systems. In all cases, there are multiple parallels between audiogenic seizures and the protective reaction of avoiding danger [28].

Consider some of the rodent lines prone to audiogenic seizures and used in laboratory practice.

Black Swiss mice are considered a good model of reflex epilepsy in humans. In many lines of mice with audiogenic seizures, hearing loss is often observed, which complicates the attribution of the pathogenesis of abnormal excitability of the brain, but the Black Swiss line lacks this disadvantage. They were obtained from crossing mice of the National Institutes of Health Swiss and C57BL/6. Later, typical audiogenic convulsions were accidentally discovered in them, susceptibility to which was inherited as a simple recessive trait [29]. The jams1 locus on the tenth chromosome, limited by the D10Mit140 marker and the Bsg (Basigin) gene, is responsible for the development of seizures in them. This region is largely similar to the region of human chromosome 19p13.3, which is involved in familial juvenile febrile seizures. The jams1 locus contains 128 known or predicted genes, one of which (*HCN2*) encodes a potential-dependent ion channel subunit. HCN channels are crucial for cell excitability, and the role of the *HCN2* subunit in the pathogenesis of generalized epilepsy and in febrile seizures in rodents is reliably known [30].

White Frings mice also have audiogenic seizures, but in combination with hearing loss. The *MASS1* gene is responsible for the development of these symptoms, which is now designated as *MGR1* with an unknown but important function for the development of the central nervous system [31]. It encodes VLGR1 (very large G-protein-coupled receptor 1), also known as MASS1 (monogenic audiogenic seizure-sensitive 1), which is an orphan receptor associated with G-protein [32].

DBA/2 mice are prone to audiogenic seizures [33]. These animals are characterized by the formation of epileptic foci in the cerebral cortex and frequent death during seizures [34]. This model is not without drawbacks: with age, fewer and fewer animals react to sound with convulsions [35].

The first Syrian hamster with audiogenic epilepsy was born spontaneously at the University of Valladolid, Spain, where this line was named GPG:Vall, and then was transferred to the University of Salamanca, where the GASH:Sal line was derived from it [36]. Salamanca hamsters of the GASH/Sal line exhibit loud-sound-induced seizures similar to generalized tonic seizures observed in patients with epilepsy. However, the genetic basis of seizures in hamsters remains unclear. Sequencing of their genome revealed 342 variants, of which 21 were classified as mutations with a high level of exposure, and functional analysis showed violations in 44 pathways, including those associated with glutamatergic synapses [37]. Hamsters are also characterized by hearing problems. Cochlear histopathology has shown the preservation of sensory hair cells with the loss of neurons of the spiral ganglion and atrophy of the vascular strip, as well as anomalies of the reticular plate. The stereocilia of the hair cells were arranged in disorder, were absent, or were distinguished by a large length. At the molecular level, patterns of abnormal expression of the genes prestin, cadherin 23, protocadherin 15, vesicular carriers of glutamate 1 (*VGLUT1*) and 2 (*VGLUT2*) were noted, indicating the upward spread of abnormal glutamatergic transmission along the primary acoustic pathway to the epileptogenic region [38].

The genetic predisposition to audiogenic epilepsy in rats was revealed back in 1906, when the Wistar Institute (USA) brought out the still existing outbred line of Wistar rats. Among them were animals that reacted to a loud sound with epileptimorphic seizures [39]. Since then, several lines of rats with audiogenic epilepsy have been created on their basis in different countries.

Genetically epilepsy-prone rats (GEPR) are two independently derived lines of GEPR-3 and GEPR-9, whose seizures differ in severity. Seizures in GEPR-3 animals are moderate, with generalized clonus of the head and forelimbs, which are typical when an epileptic focus is localized in the forebrain and occur in response to a standard sound stimulus. Seizures in GEPR-9 animals are severe, their tonic-clonic convulsions of all limbs resemble the effects of an electric shock, and the epileptic focus is localized in the brain stem. Their epilepsy is not pharmacoresistant and responds well to treatment with a variety of existing and experimental antiepileptic drugs [40–42]. Rats of the

[1] GABA – gamma-aminobutyric acid.

GEPR-3 line demonstrate a high level of anxiety, memory impairment and recognition of new objects. This, as well as the convulsive syndrome, are based on common genetic disorders [43].

Wistar rats with audiogenic epilepsy (Wistar audiogenic rat, WAR) were bred more than 25 years ago in Brazil. In response to audiogenic stimulation, they develop tonic-clonic seizures. The main neuroethological, electrophysiological, cellular and molecular protocols confirm that WARs are suitable and reliable model animals for the study of epilepsy [42].

The P77PMC rat line bred in China is genetically predisposed to audiogenic seizures, and also has a reduced level of cholecystokinin, a selective antagonist of opioid analgesia [45]. They are distinguished from ordinary Wistar rats by the expression of more than 15 genes in the cerebral cortex, among which the expression levels of 13 genes are increased compared to Wistar, and the expression levels of two genes are reduced [46].

There is also evidence of genetically predisposed to audiogenic seizures Wistar audiogenic susceptible (WAS) rats [47] and Genetic absence epilepsy rat strain (GAERS) from Strasbourg, France, which are characterized by recurrent generalized seizures in 100% of animals [48], the Dutch line Wistar Albine Glaxo/Rijswijk (WAG/Rij) [47], Japanese Wakayama epileptic rats (WER) [50], Ihara genetically epileptic rats (IGER) [51], Noda epileptic rats (NER) [52], and spontaneously epileptic rats (SER) [53].

The history of the Krushinsky–Molodkina rat line began in the late 1940s, when in 1947–1948, naturalist, cynologist, physiologist and neurobiologist L.V. Krushinsky, as well as his colleagues and students L.N. Molodkina and D.A. Fless studied the general excitability of the central nervous system and the effects of its modulation. The result of their work was Wistar rats that reacted to the sounds of the bell by running wildly with subsequent convulsions. By 1948, they had formed into a separate line, most of the animals from which showed the same reaction. Despite the closure of the laboratory and the prohibition of genetics in the USSR, Krushinsky was allowed to continue breeding rats for the study of audiogenic epilepsy [54]. Convulsions develop in response to a sound stimulus with a probability of up to 99% [55]. In the 1980s, Krushinsky–Molodkina rats were brought into an inbred state. Their genetic homogeneity is confirmed by both biochemical analyses and reciprocal skin isotransplantation [56].

Currently, in addition to the original inbred line of Krushinsky–Molodkina rats, there are two more, obtained in the 2000s by hybridization with ordinary Wistar rats and supported for more than 30 generations: Line 4 with maximum intensity of seizures and non-responsive to sound Line 0. Having similar genetics, they participate in the same experiments to study the comorbidity of epilepsy and other pathological conditions, as well as their effects on epilepsy and the brain. In addition to audiogenic seizures, Krushinsky–Molodkina rats are prone to brain hemorrhages, and can also serve as a model of cerebral circulatory disorders. Such a triad does not exist for any of the experimental animal lines described above, bred decades later [57].

Like other animals with genetically determined audiogenic epilepsy, Krushinsky–Molodkina rats differ from the ancestors of the Wistar line in a number of biochemical, behavioral and neurophysiological features. In particular, they have hyperfunction of the thyroid gland and disorders of the neurotransmitter systems of the brain, high neuroplasticity and excitability [58]. These rats are characterized by disorders of neurogenesis in the hippocampus compared to ordinary Wistar rats. In ordinary rats neuronal progenitor cells differentiate into both GABA-ergic and glutamatergic neurons, but Krushinsky–Molodkina rats gave mainly glutamatergic cells. Such a clear imbalance between excitatory and inhibitory signals in the brain with excessive activity of the excitatory glutamatergic system is one of the main mechanisms of predisposition to seizures. In their hippocampus, there is an increased expression of extracellular signal-regulated kinase 1/2 (ERK1/2) involved in the differentiation of neurons. In mice, such changes are accompanied by spontaneous seizures, in humans, high ERK1/2 activity is detected in epileptic foci of the cerebral cortex of patients with neocortical epilepsy. Krushinsky–Molodkina rats also have increased activity of other signaling pathways, for example, PKA, Akt, in humans uniquely associated with epilepsy [59, 60]. In these rats, the level of proliferation of neural progenitor cells itself is also reduced compared to Wistar rats, due to a decrease in the activity level of the Akt/Gsk3b/b-catenin/CREB signaling pathway. When proliferation is inhibited, differentiation activation is observed in animals of this line [61].

All these disorders are reflected in the behavior of Krushinsky–Molodkina rats even in the absence of sound stimulation and convulsions. This is expressed in an increased level of anxiety, a lack of social interactions, a desire to avoid unfamiliar animals and reduced locomotor activity. Rats show no interest in the study, often freeze in place. Similar behavioral changes are observed in humans with autism spectrum disorders, however, no manifestations of hyperactivity were detected in Krushinsky–Molodkina rats [62, 63].

CONCLUSION / ЗАКЛЮЧЕНИЕ

Over the past 80 years, animal research models, mainly rodents, have been key to the development of new treatments for epilepsy. In experiments with them, many anticonvulsant drugs were discovered and tested, which later entered clinical practice. All this confirms the value of animals for identifying new drugs for patients with epilepsy, including those considered drug-resistant. The

effectiveness of antiepileptic drugs demonstrates that animal models resemble human epilepsy in the nature of seizures and response to treatment, which is a logical prerequisite for any drug development program. For epilepsy, like no other disease of the central nervous system, high predictive value has been achieved in animals.

Genetic models of epilepsy, notably the rat with audiogenic seizures, have become useful tools for studying the potential of antiepileptogenic or disease-modifying drugs. The data obtained from them can be used to prevent genetic epilepsy in susceptible people, many forms of which cannot be treated with available drugs.

Any model animal is nothing more than a simple representation of a complex system, and it is impossible to reproduce all aspects of human disease in them. However, they have and will continue to play a role in identifying and developing drugs that will help drug-resistant patients.

Thus, despite the absence of epileptic seizures in humans in response to simple sound stimuli and their extreme rarity in response to complex ones, models of audiogenic epilepsy in rodents can be considered adequate for studying the mechanisms of epileptogenesis, the genetic basis of predisposition to convulsive states, the development of drug resistance and testing of new antiepileptic drugs. The neuroanatomical abnormalities, molecular mechanisms, and signaling pathways of rodent audiogenic seizures and human epilepsy are mediated by the same genes.

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