ӘЛ-ФАРАБИ АТЫНДАҒЫ ҚАЗАҚ ҰЛТТЫҚ УНИВЕРСИТЕТІ
КАЗАХСКИЙ НАЦИОНАЛЬНЫЙ УНИВЕРСИТЕТ ИМЕНИ АЛЬ-ФАРАБИ
AL-FARABI KAZAKH NATIONAL UNIVERSITY

БИОЛОГИЯ ЖӘНЕ БИОТЕХНОЛОГИЯ ФАКУЛЬТЕТІ
ФАКУЛЬТЕТ БИОЛОГИИ И БИОТЕХНОЛОГИИ
FACULTY OF BIOLOGY AND BIOTECHNOLOGY

Биология ғылымдарының докторы, профессор,
Қазақстан Республикасы Ұлттық Ғылым Академиясының корреспондент-мүшесі
ТӨЛЕУХАНОВ СҰЛТАН ТӨЛЕУХАНҰЛЫНЫҢ
70 жас мерейтойына арналған
«Биология және биотехнологияның өзекті мәселелері» атты
Халықаралық ғылыми-практикалық конференция
МАТЕРИАЛДАРЫ

МАТЕРИАЛЫ
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«Современные проблемы биологии и биотехнологии»,
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ТУЛЕУХАНОВА СУЛТАНА ТУЛЕУХАНОВИЧА

MATERIALS
of the International Scientific and Practical Conference
"The Modern Problems of Biology and Biotechnology",
dedicated to the 70th anniversary of the Doctor of Biological Sciences, Professor,
Corresponding Member of the National Academy
of Sciences of the Republic of Kazakhstan,
SULTAN T. TULEUKHANOV

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MODELING OF EPILEPTIC SEIZURES IN THE LABORATORY

Abstract: *Epilepsy is a common neurological disorder that is characterized by a persistent tendency to develop epileptic seizures. Due to the heterogeneity of this disease, the study of the molecular mechanisms of the pathogenesis of various types of epilepsy is currently one of the urgent tasks of biomedical research. Currently, it is known that in epilepsy, there is a violation of the balance of excitatory and inhibitory neurotransmitter mechanisms in the brain, which is the cause of the development of epileptiform seizures. In some cases, severe seizures can lead to further rearrangements in the brain's neuronal network and the development of acquired epilepsy. Temporal lobe epilepsy is one of the most common forms of epilepsy in humans. About 30% of cases of temporal lobe epilepsy are resistant to currently available anticonvulsant drugs, which makes the search for new therapy strategies for this disease an urgent task of neuroscience.*

Keywords*: epilepsy, models of epilepsy, neuron, kainate, hippocampus.*

Epilepsy is one of the most common chronic neurological disorders, the main feature of which is the occurrence of repeated epileptic seizures. These epileptic seizures are based on abnormal hypersynchronous excess electrical activity in the brain neurons that is not observed in the normal state [1]. In some cases, epilepsy has a genetic etiology, while in others, the development of epilepsy is caused by events such as head trauma, inflammation, stroke, neoplasms, infection, prolonged febrile seizures in childhood, and others [2]. Thus, due to the heterogeneity of this disease, the study of the pathogenesis of epilepsy and its accompanying disorders is currently a difficult task.

A few experimental models are used to study epilepsy. This is due to the fact that this disease is quite diverse in its manifestations and no model can fully convey all its features [3]. In general, according to the nature of the effect, all models can be divided into "acute" and "chronic". To simulate acute seizures, intact animals are injected with various chemical convulsive agents (pentylentetrazole, penicillin, strychnine, bicuculin, cocaine, etc.). According to the mechanism of action, chemoconvulsants are divided into blocking inhibitory mechanisms that enhance the processes of excitation, disrupt energy metabolism and inhibit the transport of ions. A single intense electrical stimulation or maximum electric shock is also used to initiate a convulsive seizure [4]. Acute models of epilepsy are mainly used to study the mechanisms underlying the development of a seizure, as well as the processes that accompany it. In addition, acute models are often used to test new antiepileptic drugs.

The chronic models of epilepsy, first of all, include the lithium-pilocarpine and kainate models. Local or systemic administration of pilocarpine (an agonist of M-cholinergic receptors) and kainate (an agonist of ionotropic glutamate receptors – KAR) to animals causes the development of a pattern of limbic seizures, and then an epileptic status, which is accompanied by brain damage. This is followed by a latent period, and then a phase of chronic seizures, characterized by the occurrence of spontaneous limbic seizures [5]. Another chronic model of epilepsy is considered to be the electric kindling model. The classic version of kindling is a multiple subthreshold electrical stimulation of various brain structures, often structures of the limbic system, as a result of which the development of epileptic seizures occurs. In addition to electrical stimulations, subthreshold chemical stimulations are also used for kindling development. Chronic models of epilepsy allow us to study the neurochemical, morphological, physiological, and behavioral disorders caused by brain damage during spontaneous seizures.

Genetic models of epilepsy represent a separate group of experimental models. The use of these models allows us to study both the work of the "excited" brain, and the mechanisms underlying the formation of such a state. These include models in which seizures either occur spontaneously or are triggered by external stimuli. Most models in which epileptiform activity does not depend on certain external influences are represented by inbred rodent lines with spontaneous absense-type activity, which is genetically determined. Hereditary models of reflex epilepsy include different lines of animals with a predisposition to seizures. These include light-sensitive baboons (*Papio papio*), which respond to visual stimuli (flashes of light) with myoclonus and tonic-clonic seizures, as well as audiogenic rats and mice, which develop generalized convulsive seizures in response to a sound stimulus of a certain intensity and frequency [6].

For the first time, audiogenic convulsive activity was observed in rats of two outbred lines (populations) – Wistar and Sprague-Dawley. Subsequently, in different countries of the world, with the help of breeding and closely related crossing, lines of animals were created that demonstrate stable audiogenic seizures. Currently, the most widely known hereditary models of audiogenic epilepsy are rats of the KM, GEPR-9, GEPR-3, and WAR lines [7]. At the University of Arizona, a line of GEPR rats genetically predisposed to audiogenic seizures, including 2 subtypes that differ in response to a sound stimulus, was derived from an outbred line of Sprague-Dooley rats. Thus, in response to sound stimulation, GEPR-3 rats develop clonic seizures, while GEPR-9 rats develop tonic seizures. On the basis of the outbred line of Wistar rats, several independent lines were derived that respond to sound stimulation with a convulsive seizure. These include the Wistar audiogenic rats (WAR) rat line, which was obtained in Brazil, as well as the KM rat line, which was bred in the 60s in Russia based on the Moscow State University by L.V. Krushinsky, L.N. Molodkina and D.A. Fless [8].

In the experiments of I.B. Fedotova and A.F. Semiokhina, it was shown that a stable epileptiform convulsive reaction to sound in rats of the KM line is established by 3 months of age [9]. For the KM rats, a fairly short latent period of about 2-5 seconds is characteristic, after which a convulsive seizure develops, characterized by a wild run stage, clonic-tonic convulsions, and postictal depression. After the audiogenic seizure is complete, the CM rats have a catalepsy state, which is characterized by" waxy flexibility " of the body muscles and complete areflexia [8].

As a result of a number of studies, it was shown that the main structure responsible for the generation of audiogenic convulsive activity in KM rats is the medulla oblongata. Thus, Akulichev and co-authors found an increase in c-foc expression in the medulla oblongata as early as 15 minutes after the seizure, while in other parts of the brain (in the cerebellum, hippocampus, and new cortex), increased expression was detected at a later time [10]. This assumption is also supported by electrophysiological studies, in which it was shown that in the early stages of a seizure, epileptiform discharges of the "peak-wave" type are registered in the medulla oblongata of KM rats. In GEPR and KM rats, it was demonstrated that another critical structure involved in the development of audiogenic convulsive seizures is the lower bicolm [11]. It is shown that the increase in neural discharges in the lower two-lobe is accompanied by the onset of motor excitation. After this, the epileptiform activity spreads to the reticular nucleus of the bridge and the periconvex gray matter, which corresponds to the beginning of the clonic-tonic stage of a convulsive seizure. Then, after the completion of the convulsive seizure, in all the structures mentioned above, except for the reticular nucleus of the bridge, there is a decrease in electrical activity. In the forebrain, no epileptiform activity was detected in a single audiogenic convulsive seizure. However, with repeated sound stimulations, the expansion of the epileptic network was noted due to the involvement of the structures of the limbic system and the new cortex. This phenomenon is called audiogenic kindling [12]. Audiogenic kindling is an adequate model for the study of epileptogenesis (the spread of epileptiform activity in the brain), as well as the associated processes.

In rats with a hereditary predisposition to audiogenic epilepsy, the state of the brain's neurotransmitter systems has been studied in some detail. It was shown that the levels of dopamine and 3,4-dioxyphenylacetic acid in the hypothalamus and striatum were significantly higher in KM rats compared to Wistar rats without convulsive activity. However, when analyzing the ratio of dopamine and its metabolites, it was found that the KM rats have a defect in dopamine metabolism. Elevated levels of dopamine, norepinephrine, and epinephrine, as well as a decrease in the rate of dopamine metabolism, were also observed in the adrenal glands of KM rats. At the same time, in contrast to Wistar rats, the basal state showed an increased content of serotonin and its metabolite, 5-hydroxyindolacetic acid, as well as an increased level of serotonin metabolism in the temporal cortex, hippocampus, and medulla oblongata (but not in the striatum). Changes in biogenic amine ratios in the brain have also been demonstrated in other models of audiogenic epilepsy.

Increased levels of aspartate, glutamate, and glycine (by 35-45 %) and reduced levels of GABA in KM rats compared to Wistar rats were shown in the medulla oblongata. In the striatum and in the temporal cortex, on the contrary, in the KM rats, an increased content of GABA was observed. The level of glycine in KM rats compared to Wistar rats was increased in the temporal cortex but decreased in the hippocampus [13]. Thus, the literature data indicate that rats with increased sensitivity to sound in the basal state are characterized by changes in the levels of biogenic amines of the brain, neurotransmitter amino acids and their metabolites. The shown neurochemical features of these rats can, on the one hand, contribute to the development of audiogenic seizures, and on the other, lead to disorders in the regulation of the neuroendocrine system.

One of the promising approaches may be preventive therapy after a potentially epileptogenic event, aimed at preventing the development of epilepsy. Unfortunately, at the moment, there is not enough data on the molecular mechanisms of induced epileptogenesis to develop such an approach. Although there is evidence of the involvement of calcium-permeable kainate and AMPA receptors in the early stages of epileptogenesis and the possible role of calcium-permeable kainate and AMPA receptors in the development of further pathological changes requires further study. This makes calcium-permeable kainate and AMPA receptors a promising target for the pharmacotherapy of epilepsy, but their role in seizures of various etiologies requires further study.

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ЗЕРТХАНАЛЫҚ ЖАҒДАЙДА ЭПИЛЕПСИЯЛЫҚ ҰСТАМАЛАРДЫ МОДЕЛЬДЕУ

Аннотация: *Эпилепсия – бұл эпилепсиялық ұстамалардың пайда болуына тұрақты бейімділікпен сипатталатын ең кеңтаралған неврологиялық ауру. Аурудың гетерогенділігіне байланысты эпилепсияның әртүрлі типтері патогенезінің молекулалық механизмдерін зерттеу бүгінгі таңдағы биомедициналық зерттеулердің өзекті міндеттерінің бірі болып табылады. Қазіргі уақытта эпилепсиялық құрысулар кезінде мидағы қоздырушы және тежеуші нейротрансмиттерлік механизмдер теңгерімінің бұзылатындығы анықталды, бұл эпилептиформалық ұстамалардың дамуына себеп болады. Кейбір жағдайларда ауыр құрысу ұстамалары мидың нейрондық желісінде одан әрі қайта құрулармен және жүре пайда болған эпилепсияның дамуына әкелуі мүмкін. Адамдарда эпилепсияның ең кең таралған түрлерінің бірі – самай эпилепсиясы. Самай эпилепсия жағдайларының шамамен 30%-ы қазіргі кездегі құрысуға қарсы препараттарға төзімді, бұл аталған ауруды емдеудің жаңа стратегияларын іздеуді нейробиологияның өзекті міндеттерінің айналдырды.*

Түйін сөздер: *эпилепсия, эпилепсия модельдері, нейрон, кашнат, гиппокамп.*

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МОДЕЛИРОВАНИЕ ЭПИЛЕПТИЧЕСКИХ ПРИПАДКОВ В ЛАБОРАТОРНЫХ УСЛОВИЯХ

Аннотация: *Эпилепсия распространенное неврологическое расстройство, характеризующееся стойкой склонностью к возникновению эпилептических припадков. В связи с неоднородностью этого заболевания изучение молекулярных механизмов патогенеза различных видов эпилепсии в настоящее время является одной из актуальных задач биомедицинских исследований. В настоящее время известно, что при эпилепсии наблюдается нарушение баланса возбуждающих и тормозных нейромедиаторных механизмов в головном мозге, что является причиной развития эпилептиформных припадков. В некоторых случаях тяжелые судорожные припадки могут привести к дальнейшим перестройкам в нейрональной сети мозга и развитию приобретенной эпилепсии. Височная эпилепсия – одна из наиболее распространенных форм эпилепсии у людей. Около 30% случаев височной эпилепсии резистентны к имеющимся в настоящее время противосудорожным препаратам, что делает поиск новых стратегий терапии этого заболевания актуальной задачей нейробиологии.*
Ключевые слова: *эпилепсия, модели эпилепсии, нейрон, каинат, гиппокамп.*

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HAEMATOLOGICAL AND BIOCHEMICAL PARAMETERS IN CHILDREN WITH DIFFERENT FORMS OF ENCEPHALOPATHY

Abstract: *Encephalopathy is a group of diseases whose main manifestation is the gradual degeneration of brain tissue. To treat the disease, it is important to eliminate the underlying factor that gradually destroys the brain. This may be arterial hypertension, atherosclerosis, insufficient liver or kidney function, craniocerebral injuries, venous outflow disorders, diabetes mellitus and many other causes. This article is therefore devoted to the evaluation of haematological and biochemical parameters in children with encephalopathy. The results of biochemical and haematological blood parameters, as well as changes in the respiratory and cardiovascular systems before and after rehabilitation are presented. The study of encephalopathy in children and adults caused by cardiovascular pathology, metabolic disorders and craniocerebral trauma is a priority in modern paediatrics and neurology. The results of biochemical and haematological indexes research before and after rehabilitation showed the positive tendency.*
Keywords*: oxidative stress, mitochondrial dysfunction, hematological and biochemical blood parameters, neurodegenerative disorders.*

Mitochondria contain numerous redox transporters and centres involved in redox reactions. Mitochondria are capable not only of oxygen reduction to water, but also of one-electron reduction of oxygen to the anion radical superoxide, a precursor of other reactive oxygen species. An imbalance between the production of reactive oxygen species and the activity of antioxidant control systems results in a state of intracellular oxidative stress, which is accompanied by an increased rate of free radical formation, often leading to cell death. Oxidative stress, which leads to oxidative damage and mitochondrial DNA dysfunction, appears to determine the severity of neurodegenerative disorders. One of the most common neurodegenerative diseases is encephalopathy, which is characterised by reduced nerve tissue volume and impaired brain function.

In this regard, it is of interest to study biochemical and haematological parameters in children with encephalopathy, as well as changes in the respiratory and cardiovascular systems before rehabilitation and after rehabilitation.

Oxidative stress is a failure of the body's antioxidant system, in which cells are exposed to excessive levels of reactive oxygen species and other free radicals. This leads to selective death of specialized cells, decreased

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