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ФИЗИОЛОГИЧЕСКИЕ КОРРЕЛЯТЫ НЕЙРО- И МАГНИТОСТИМУЛЯЦИИ В ТЕРАПИИ ЭПИЛЕПСИИ

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В обзоре литературы рассмотрены исследования нефармакологических методов терапии эпилепсии, среди которых электростимуляция блуждающего и тройничного нерва, воздействие магнитным полем и транскраниальная магнитная стимуляция (ТМС). Коррелятами эффективности электро- и магнитостимуляции являются электрофизиологические показатели, клинические данные и влияние на психические и когнитивные функции. Использование ритмической транскраниальной магнитной стимуляции в дополнение к противоэпилептическим препаратам имеет свое обоснование. Согласно современным представлениям и результатам экспериментальных исследований, механизм модуляторных ингибиторных изменений связан с возможностью ритмической ТМС вызывать долговременную синаптическую депрессию или долговременную потенциацию. Эти длительно существующие феномены, возможно, лежат в основе противосудорожных эффектов низкочастотной магнитной стимуляции. Включение в исследовательские работы физиологов, нейрофизиологов будет способствовать решению столь важной задачи как исследование физиологических механизмов эффективности нефармакологического электро- и магнитного воздействия при эпилепсии.

Ключевые слова: *электростимуляция блуждающего и тройничного нерва; транскраниальная магнитная стимуляция; магнитное поле; эпилепсия.*

PHYSIOLOGICAL CORRELATES OF NEURO- AND MAGNETIC STIMULATION IN THERAPY OF EPILEPSY

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In the literature survey, non-pharmaceutical methods of therapy of epilepsy are considered including electrostimulation of vagus nerve, exposure to magnetic field and transcranial magnetic stimulation (TMS). Correlates of the effectiveness of electro- and magnetic stimulation are electrophysiological parameters, clinical data and influence on the mental and cognitive functions. Use of repetitive transcranial magnetic stimulation in addition to antiepileptic drugs has a certain ground. According to modern understanding and the results of experimental studies, the mechanism of modulator inhibitory alterations is associated with a potential of TMS to cause long-term synaptic depression or long-term potentiation. These long-lasting phenomena probably underlie anticonvulsant effects of low frequency magnetic stimulation. Inclusion of physiologists and neurophysiologists into the research will permit to solve such an important problem as a study of physiological mechanisms of the effectiveness of non-pharmacological electro- and magnetic action in epilepsy.

Keywords: *vagus and trigeminal nerves stimulation; transcranial magnetic stimulation; magnetic field; epilepsy.*

The problem of the influence of pharmacological drugs on functions of the central nervous system, on psychophysiological parameters, mental sphere and cognitive functions, including negative effects of antiepileptic drugs (AEDs), does not lose its importance. Quite often, negative consequences of therapy caused by side effects, overweigh the positive result of rapid relief of attacks. Therefore, search for non-drug therapeutic techniques remains an urgent task. These include vagus nerve stimulation [1,2] and transcranial magnetic stimulation (TMS) [3,4]. There are also well known other methods of magnetic therapy – use of magnetic influence in the form of static, alternating, pulsed and other kinds of magnetic fields [5,6].

The most commonly occurring alternating magnetic field (AMF) is sinusoidal magnetic field generated by an inductor supplied from the city mains or from a special sine-wave generator. In modern magnetic therapy, along with sinusoidal form, other forms of magnetic fields are used. To enhance the therapeutic effect of magnetic fields and of the biological effects, various additional techniques are often used in magnetic therapy: combinations of alternating field with static or with other kinds of magnetic fields.
Besides, magnetic field may be pulsed or continuous, high and low frequency. Magnetic therapy may be local and general. The most common is local action, often with successive action on several zones.

Studies of application of the method of magnetic therapy in epilepsy show the potential of positive influence of magnetic fields on the condition of a patient, however, these studies are scarce. Thus, C. Rivadulla, et al. (2018) showed in their work that static magnetic field generated by a stimulator in the region of the cortex (within the range of 0.3-0.5 T), as a rule, produces inhibitory effect on epileptogenesis in animals and humans [7].

There exist many devices operating on the principle of magnetic fields (generators), but, in the manuals to these magnetotherapy devices there is no mention of epilepsy either in indications or in contraindications. This means that these devices did not undergo extensive trials in the therapy of epilepsy.

G.V. Selitsky et al. (1996) in their work used local alternating magnetic fields (alternating exposure of wrists of both hands) in the double-blind study and recorded parameters of the bioelectrical activity of the brain. It was shown that application of the alternating magnetic field at therapeutic doses both in healthy individuals an in patients with epilepsy induced changes in the parameters of the bioelectrical activity, increased synchronization in alpha- and theta-rhythm, with more evident changes in the right hemisphere of the brain [5].

The speed of the blood flow via the large cerebral vessels generates electric field that may be picked up from the head surface [8]. Accordingly, external magnetic influence alters not only parameters of the cerebral blood flow, blood supply to the brain and delivery of oxygen to the brain calls, but also influences peculiarities of the bioelectrical activity of the brain, that permits to use this method for diagnosis of the magnetic field effect.

Both increase and decrease (hypogeomagnetic field, HGMF) produces influence on the parameters of the bioelectrical activity on encephalogram (EEG). A study of the influence of HGMF on the bioelectrical activity of the brain in epilepsy showed increase in synchronization of the bioelectrical activity and increase in the spectral power in the regions associated with the epileptic focus [9,10].

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Another actively used method, besides the effect of magnetic field, is neurostimulation. Electrical stimulation (ES) of the peripheral and central nervous system requires use of implanted electrodes and electric field generator. Many-year research in this direction showed effectiveness of neurostimulation. Of most interest are factors that influence stability of the positive results. It is known that it is the worsening of the results in catamnesis that is one of sticking points on the way to a wider use of the method of neurostimulation [11].

According to the data of joint research of the University of California in Los-Angeles and the University of South California, external stimulation of the trigeminal nerve is used in treatment of pharmacoresistant forms of epilepsy in adults and children over 9, and also of depression disorders which often accompany this diagnosis [12].

Neurostimulation is primarily being developed as therapy for patients with pharmacoresistant epilepsy who are not candidates for surgical treatment of epilepsy. Stimulation of the vagus is the most common approach that has been used in more than 70 000 patients worldwide within the recent 15 years, with the proven successive reduction of the convulsive readiness by more than 50% in more than half of the patients. Besides, in about 5% of patients a complete remission of attacks was achieved. Percutaneous stimulation of the vagus and trigeminal nerve proved to be clinically effective, but, however, it remains necessary to theoretically substantiate use of these methods in further studies [13].

Transcranial magnetic stimulation (TMS) is a method of neurostimulation and neuromodulation based on use of magnetic field generated by electromagnetic induction of the electric field and strictly targeted at a particular region of the brain. TMS was first proposed by A.T. Barker (1985) and at present is widely used worldwide [14].

Within the recent 10-20 years a new technology was introduced to clinical practice – repetitive TMS (rTMS) – a kind of TMS with generation of a train of pulses at 1 to 100 Hz frequency. There exist two modes of rTMS: low frequency and high frequency ones. Low frequency magnetic stimulation causes reduction of excitability of the cortical neurons, and high frequency stimulation causes increase in their excitability [15].

Stimulation of the brain which may in some cases provoke seizure attack, and may also be a method of treatment for epilepsy. First of all this refers to pharmacoresistant forms of epilepsy which make about 20% of the primarily generalized forms and up to 60% of the focal forms [16].

In the PubMed data base there exist a large amount of publications on application of rTMS in epilepsy. Many of them demonstrate contradictory results except [17,18] which reliably show effectiveness of rTMS in reduction of the rate of attacks as compared to placebo.

In meta-analysis of 2011 that included 11 controlled studies with the total number of patients 164 [19], a conclusion was made about a reliable reduction of the rate of attacks with low frequency stimulation of the epileptic focus in neocortical epilepsies and cortical dysplasias.

T.V. Dokukina et al. (2018) showed that application of pulsed magnetic therapy in complex treatment of patients with epilepsy and with related mental disorders ensures evident and stable improvement of the parameters of memory and attention [20]. In 94% of patients whose treatment complex included pulsed magnetic therapy, cognitive functions recovered to the age-related norm, or significantly improved, as compared patients who did not receive magnetic therapy or received imitation of magnetic therapy. The most evident improvement was achieved in the parameter of depletion of mental processes in 1 month and 1 year, and in the parameter of retaining information in 1 month.

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Pulsed magnetic field was applied with exponential pulses of 15 msec duration at 10 Hz repetition rate. Induction of magnetic field was 50 mT. Inductors with the operating surface 20 cm^2 were bytemporally fixed with inductor holders and were placed directly over the top of the auricle of a patient. The procedure was performed in the horizontal position. Exposure time was 15 minutes. The treatment course included 10-12 procedures. Fake magnetic therapy was conducted with the device disconnected from the mains [20].

Some modes of rTMS (for example, low frequency rTMS < 1 Hz, or continuous rTMS in theta-wave mode) may suppress excitation in the cortex probably through modulation of the activity of GABA and of increase in the convulsive readiness threshold [14]. Therefore, it is possible to explain the effect of rTMS to rapidly alleviate an attack, for example, in focal epileptic status, in permanent partial epilepsy [21]. It is possible to use TMS in local epilepsy for direct action on the cortical focus of epileptic activity, or on the adjacent cortical zone in case of subcortical focus; here, medial parts of the temporal lobe, for example, are inaccessible for stimulation. Many, but not all studies demonstrated reduction of the frequency of epileptic attacks on exposure to TMS, besides, not all of them were randomized placebo-controlled studies [22,23]. In some cases low effectiveness of rTMS was attributable to non-precise delivery of the field to the epileptogenic focus, therefore, modern navigation systems will probably permit to improve the results of therapy [24].

In the literature survey [25] 7 studies were analyzed involving 230 patients. It was shown by the authors that only 2 of 7 works presented statistically significant reduction of the frequency of attacks as compared to the background level (72 and 78.9%, respectively). The authors conclude that because of impossibility to compare methods of implementation of studies, the difference in evaluations and records of the results, it is difficult to make a conclusion about the effectiveness of the method for reduction of attacks in use of rTMS. Safety of the procedure and a low amount of side effects in the form of headaches, dizziness and tinnitus was shown.

Researchers [26] presented the analysis of the results of clinical, electroencephalographic (EEG) and neurovisualization studies of 19 patients with epilepsy who were given a course of rTMS along with intake of anticonvulsants at subtherapeutic doses. It was found that application of low intensity rTMS at 1 Hz frequency over the temporal zone in combination with anticonvulsants can reduce the number of epileptic attacks per week by 91.9% during the course and by 75% in a month after completion of the combined treatment. A course of treatment with rTMS leads to reduction of the amount of interictal discharges and of the amount of patients with interictal epileptic EEG-phenomena not only in the period of stimulation, but also within the subsequent 4-12 weeks. Magnetic stimulation causes long-term changes on the EEG – increase in the index and improvements of the frequency and spatial structure of alpha-rhythm, reduction of the index of theta-rhythm and of pathological beta-rhythm, reduction of the quantity and size of foci of theta- and beta-rhythms. Application of low frequency and low intensity rTMS in complex treatment of epilepsy with subtherapeutic doses of anticonvulsants permits to avoid side effects and ensures high anticonvulsant effectiveness. The obtained results show 91.9% reduction of the frequency of attacks during the course of rTMS and 75% reduction within the subsequent 4 weeks.

The authors [27] presented a systematic survey of 46 publications with a detailed analysis of the influence of rTMS on the course of epilepsy. Of the total amount of examined patients, 18.3% demonstrated side effects, which were mild in 85% of patients. Headaches or dizziness were noted in 8.9% of patients. The risk of attacks was recorded in 2.9% of patients. Only in one patient an at-

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tack was noted that was atypical as compared to the initial background data of study. On the whole, the authors came to the conclusion that the risk of initiation of an attack in patients was low and side effects were similar to those in healthy tested individuals.

Selection of individuals for participation in rTMS procedure requires use of a special questionnaire that includes 15 questions and permits screening [28]. Contraindications to the given type of exposure are, in particular, the presence of metal objects in the vicinity of magnetic coil (hearing implants, pumps, implanted electrodes), history of epilepsy (if it is not special treatment of TMS epilepsy), vascular, traumatic, tumorous or infectious lesions of the brain. In case of presence of an implant in a patient, a probable extent of heating or of magnetization is obligatorily determined for each specific stimulation protocol and for the type of coil used. The most common side effects of TMS are moderate local pain or discomfort in the exposure zone (up to 40%) and headaches (up to 30%) that is associated with stimulation of the branches of the trigeminal nerve and with muscular spasms. Painful sensations in rTMS are similar to those in repeated stimulation of the peripheral nerves of the face or scalp which in some individuals leads to headaches due to tension of muscles. Besides, magnetic stimulation generates high frequency noise that may induce a short-term alteration of the hearing threshold. In literature separate cases of development of epileptic attacks after exposure to TMS are reported: in depression with the underlying intake of antidepressants, in tinnitus. The risk of their development is not high making only 1.4% even in patients with epilepsy [28].

Use of rTMS in addition to AEDs is substantiated. According to modern understanding and the results of experimental studies, the mechanism of modulator inhibitory alterations is associated with the potentiality of rTMS to evoke a long-term synaptic depression or long-term potentiation. These long-lasting phenomena probably underlie anticonvulsive effects of low frequency magnetic stimulation [29].

Mechanisms of rTMS are associated with its potentiality to induce effects of long-term postsynaptic inhibition in the excitatory neurotransmitter systems and to reduce excitability of neurons through activation of voltage-dependent channels [30,31].

Repetitive TMS causes increase in the extracellular concentration of dopamine and glutamate in the regions of the brain controlling circadian biological rhythms and zones responsible for addictive behavior [32].

Use of intracerebral microdialysis *in vivo* in rats after repetitive TMS over the frontal lobes permitted to detect increased liberation of taurine, aspartate and serotonin in the paraventricular hypothalamic nucleus. In the blood of rats after rTMS increased concentration of cholecystokinin was found that influences metabolism of neurotransmitters, dopamine and of the brain neurotrophic factor derivate that possesses antidepressant effect. It was shown that rTMS can influence GABA- and glutamine-ergic systems of the brain [33].

High-resolution EEG showed an immediate response in the place of stimulation with the subsequent propagation of excitation within 5-10 msec to the ipsilateral and within 20 msec – to the contralateral motor zones [34]. Thus, it is necessary to take into account the factor of functional asymmetry of the exposure. The obtained data evidence reduction of the cortical excitability after application of low frequency rTMS which was the ground for use of magnetic stimulation in treatment of patients with focal dystonia, epilepsy, auditory hallucinations [34].

M. Kinoshita, et al. used rTMS at 0.9 Hz frequency within 5 days in 7 patients with pharmacoresistant extratemporal epilepsy. Frequency of all attacks decreased 19.1%, with this, simple partial attacks became 7.4% more rare, and complex partial attacks – 35.9% more rare [35].

R. Cantello, et al. used rTMS of 0.3 Hz frequency with the intensity of 100% of the maximal threshold, generated by a round inductor located above *vertex*, within 5 days in 43 patients with focal neocortical epileptic syndromes. Reduction of the number of attacks was noted as compared to the period before magnetic stimulation and was most expressed on the 3^{d} week after a course of rTMS. In this study 1/3 of patients showed reduction of the number and duration of paroxysmal epiactivity in EEG [36]. In a study with a longer course of rTMS (2 weeks) over the epileptogenic zone (0.5 Hz, 120% of maximal threshold) a reliable 71% reduction of attacks was noted within this period, and 50% reduction within the next two months [24].

O.V. Kisten and V.V. Evstigneev (2014) showed effectiveness of combined therapy (AEDs with rTMS) that depend on some factors with the most favorable ones being absence of complex partial attacks, frequency of attacks not more than three times per week, duration of the disease less than 10 years and absence of significant structural damages according to the data of diffusion tensor magnetic resonance imaging (MRI) [37]. The presence of these predictors permits to conduct rTMS with a reliable effectiveness.

The data published nowadays with all limitations taken into account enabled the European group of experts to assign C class of evidence ('probably effective') to low frequency mode of stimulation of the epileptic focus (located in the right or left cerebral hemisphere) or in direct vicinity of cortical dysplasia [18].

The factor of asymmetry of rTMS is of significance not only for therapy of epilepsy and for reduction of the number of attacks, but also for therapy of concomitant affective disorders. Thus, researchers [38] studied mechanisms of organization of hemispheric asymmetry of emoji in healthy individuals and in patients with epilepsy. The research was conducted in three groups: the 1st and 2nd groups were practically healthy individuals. The 3^{d} group involved patients with idiopathic epilepsy. The 1st and the 3^{d} groups received transcranial magnetic stimulation on the right and left frontal area and the 2nd was control group (fake stimulation). It was shown that transcranial magnetic stimulation of the right frontal area led to a reliable increase in time of examining negative photos, and to reduction of the time of examining positive photos. Transcranial magnetic stimulation of the left frontal area in healthy individuals and in patients with epilepsy led to a reliable increase in the average time of examining positive photos and to reduction of the average time of examining negative photos. The right hemisphere in healthy individuals and in patents with epilepsy is to a larger extent associated with negative emoji, and the left hemisphere – with positive emoji.

Conclusion

Thus, in non-medicinal treatment of epilepsy, vagus stimulation, transcranial magnetic stimulation are widely used, while static, alternating, pulsed and other kinds of magnetic fields generated by magneto-therapeutic devices of peripheral and central application are not yet sufficiently studied. Static magnetic field generated by a stimulator in the region of the cortex at 1 cm distance (0.3-0.5 T) produces an inhibitory effect on epileptogenesis while a stimulator of peripheral action enhances synchronization of epileptic activity. While neurostimulation has a long history and an evidence basis, and vagus stimulation at present finds increasing use in non-invasive (percutaneous) devices [39] (thus reducing the risk of inflammatory reactions and other side effects), the use of repetitive transcranial magnetic stimulation in addition to antiepileptic drugs, with taking into account all limitations, permitted the European group of experts to assign C evidence class ('probably effective') to low frequency mode of stimulation of the epileptic focus with its localization in the cortex or close to cortical dysplasia. According to modern understanding and results of experimental studies, the mechanism of inhibitory alterations is associated

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with the potential of repetitive transcranial magnetic stimulation to evoke a long-term synaptic depression or long-term potentiation. These long-standing phenomena are likely to underlie anticonvulsive effects of low frequency magnetic stimulation. In local epilepsy it is possible to directly act on the cortical focus of epileptic activity by repetitive transcranial magnetic stimulation, and in case of subcortical focus – on the adjacent zone using the data of functional localization (electroencephalogram) and an organic component (magnetic resonance imaging, positron emission tomography) of the epileptic focus.

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