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ENHANCED ANTICONVULSANT EFFICACY OF INTERLEUKIN RECEPTOR BLOCKADE FOLLOWING LEVETIRACETAM USE

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The purpose of the study was to determine the principal possibility of enhancement of the anticonvulsant effect of interleukin receptor blockade by levetiracetam in chronic experimental epileptogenesis. Experimental studies were performed on models of acute generalized and chronic epileptic activity. Rats were treated with systemic and intracerebroventricular injections of a recombinant interleukin receptor blocker, administered in combination with levetiracetam. Interleukin receptor activity block was shown to protect animals from acute generalized and chronic seizures during kindling and postkindling. The revealed recombinant interleukin receptor antagonist, when administered systemically and intracerebroventricularly, shows anticonvulsant efficacy that is enhanced by levetiracetam. The revealed anticonvulsant effect is observed in acute generalized pentylenetetrazole- and kainic acid-induced seizures, as well as in a chronic convulsive syndrome under intra-hippocampal blockade of interleukin receptors. The obtained results indicate that the inflammatory response is involved in the pathogenetic mechanisms of seizure syndrome. The author concludes that the fundamental possibility of increasing anticonvulsant therapy efficacy in patients with refractory epilepsy was achieved through the co-administration of drugs that block neurotransmitter systems responsible for the initiation and propagation of excessive bioelectrical activity.

Key words: convulsive syndrome, kindling, postkindling, cytokines, recombinant antagonist of interleukin-1 receptors, levetiracetam, neurotransmitter systems, pathogenetic mechanisms.

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ПОСИЛЕННЯ ПРОТИСУДОМНОГО ЕФЕКТУ ВІД БЛОКАДИ ІНТЕРЛЕЙКІНОВИХ РЕЦЕПТОРІВ ПРИ ЗАСТОСУВАННІ ЛЕВЕТИРАЦЕТАМУ

Метою дослідження було визначення принципової можливості підсилення протисудомної дії блокади інтерлейкінових рецепторів під впливом леветирацетаму при хронічному експериментальному епілептогенезі. Експериментальні дослідження проведено на моделях гострої генералізованої та хронічної епілептичної активності. Щурам застосовували системні та внутрішньомозкові введення рекомбінантного блокатора інтерлейкінових рецепторів на тлі введення леветирацетаму. Показано, що блокада активності інтерлейкінових рецепторів спричиняє захист тварин від гострих генералізованих та хронічних судом в стадії кіндлінгу та посткіндлінгу. При цьому протисудомна ефективність системного та внутрішньомозкового введення рекомбінантного антагоністу інтерлейкінових рецепторів підсилюється при застосуванні леветирацетаму. Доведений протисудомний ефект реалізується за умов гострих генералізованих судом, ініційованих пентиленететразолом і каїновою кислотою, а також за умов хронічного судомного синдрому при внутрішньогіпокампальній блокаді інтерлейкінових рецепторів. Отримані результати свідчать про залучення запальної реакції в патогенетичні механізми судомного синдрому. Автори висловлюють про досягнуту принципову можливість підвищення ефективності протисудомної стратегії у хворих на резистентну епілепсію шляхом сумісного введення фармакологічних препаратів, які блокують активність нейромедіаторних систем, відповідальних за ініціацію та розповсюдження надмірної біоелектричної активності по мозку, та спричиняють протизапальні ефекти.

Ключові слова: судомний синдром, кіндлінг, посткіндлінг, цитокіни, рекомбінантний антагоніст інтерлейкін-1 рецепторів, леветирацетам, нейротрасмітерні системи, патогенетичні механізми.

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According to the International League Against Epilepsy, epilepsy is a neurological disorder characterized by clonic-tonic recurrent and unpredictable seizures, which is believed to initiate due to complex dysregulation of receptors, neurons, and neurotransmitter interactions [15]. This severe neurological disorder affects approximately 50 million people worldwide [11]. Epilepsy development and manifestation are caused by a critical combination of factors and processes that collectively contribute to the disease pathogenesis [5]. These items may include changes in neuronal excitability, neurotransmitter imbalances, synaptic disturbances, and disruptions in interneuronal connections [1].

Inflammation as a pathogenetic trigger of epileptogenesis has been investigated since the late 1990s [14]. Seizures were shown to be induced in conditions of high concentrations in brain areas involved in epileptic activity (EpA) initiation and propagation. In particular, the inflammatory response after seizures both chemical and electrical initiation triggered by microglia and astrocytes through increased synthesis of interleukin -1b (IL-1), IL-6 and tumor necrosuis factor-α followed by a cascade of inflammatory neurons and endothelial cells release, such as NFkB, COX-2, the complement system, chemokines, acute phase proteins, etc. [2, 9, 14].

The investigation of cytokine receptor expression in seizures provided priceless insight into the mechanisms of cytokine-receptor interactions. It was shown that the proinflammatory cytokine IL-1β mediates its biological effects by binding its specific receptor, the interleukin-1 receptor type 1 (IL-1R1) [14]. Such an interaction activates NF-κB and MAPK intracellular pathways, which increase the production of inflammatory mediators and the release of immune cells, thereby causing inflammation, fever, and pain across a range of clinical conditions, from infectious to autoimmune diseases.

Intracerebral IL–1β injection in rodents was shown to increase seizure frequency induced by bicuculline and kainic acid, enabling investigation of various neurotransmitter mechanisms of epileptogenesis [10]. In contrast, intracerebroventricular administration of the IL–1β receptor antagonist revealed a powerful anticonvulsant effect in mice [10, 14].

The anticonvulsant efficacy of interleukin receptor blockade with recombinant IL–1 receptor antagonist (RAIL) was demonstrated in the kindling model of epilepsy [13]. We performed a series of experimental trials to elucidate the potential for enhancing anticonvulsant efficacy by blocking the IL–1 receptor and using the conventional antiepileptic drug levetiracetam (LVT).

It is worth determining the anticonvulsant efficacy of LVT administration against premature blockade of IL-1 receptors in conditions of acute generalized EpA, as well as in the kindling and post-kindling stages, the latter of which is an experimental model of the resistant form of epileptogenesis [3].

The purpose of the study was to determine the principal possibility of enhancement of the anticonvulsant effect of interleukin receptor blockade by levetiracetam in chronic experimental epileptogenesis.

Materials and methods. Experimental studies were performed on 460 male Wistar rats aged 6 months. Animals were kept at a constant room ambient temperature of 21–24 °C, 60 % relative humidity, and with a 12-hour artificial dark/light cycle. Male rats were chosen to avoid the endocrine influences typical of females on ionizing radiation. The animals underwent a seven-day adaptation period before the start of the trials. Rats were housed in plastic cages with metal mesh lids, six animals per cage, with free behaviour and free access to food and water. Wood shavings were used as bedding, which was changed at least once every 48 hrs. The cages were not equipped with any additional materials. The basic requirements of the International Animal Research Reporting Protocols ARRIVE 2.0 were used in these experimental trials.

The maintenance, handling and manipulation of animals were carried out in accordance with the "General Ethical Principles of Animal Experiments" approved by the Seventh National Congress on Bioethics (Kyiv, 2019) and was guided by the recommendations of the European Convention for the Protection of Vertebrate Animals for Experimental and Other Scientific Purposes (Strasbourg, 1985), the methodological recommendations of the State Clinical Research Center of the Ministry of Health of Ukraine "Preclinical Studies of Drugs" (2001) and the rules for the humane treatment of experimental animals and conditions approved by the Bioethics Commission of Odesa National Medical University (No 16, October 4, 2023).

Two models of convulsive syndrome were used: acute generalized convulsive reactions, kindling chronic convulsive syndrome, and postkindling.

Generalized convulsions were induced in rats by i.p. picrotoxin (PCT, 2.0 mg/kg), pentylenetetrazol (PTZ, 40 mg/kg), and kainic acid (KA; 15 mg/kg; all used convulsants are of "Sigma-Aldrich", Germany) administration. The control groups' animals in these conditions were injected with similar volumes of 0.9 % physiological solution.

Kindling was induced by 24–day PCT administration at a subthreshold dose of 0.9-1.1 mg/kg [7]. The postkindling stage, which is considered a stage of enhanced convulsive resistance, developed 14 days after the kindling formation [7].

The following groups were randomized in accordance with used thee models of generalized seizure reactions induced by PCT, PTZ and KA, correspondently: group 1 – control (administration of 0.9 % physiological solution, n=10), group 2 – administration of convulsants and LVT (i.p., 200 mg/kg; "Tokyo Chemical Industry Co. Ltd", Japan, n=12), groups 3 and 5 – i.p. administration of convulsants with human RAIL at doses of 7.5 mg/kg and 10.0 mg/kg (dissolved in 0.2 % sodium hyaluronate in phosphate-buffered saline, pH=7.4; "Amgen", USA; n=12 each), groups 4 and 6 – i.p. administration of convulsants, RAIL in both doses and LVT (n=12 each).

The following groups were randomized while investigating both kindling and postkindling induced chronic convulsive syndrome on the background of RAIL intracerebroventrical (icv), intranigral and intrahippocampal microinjections: group 1 – control (administration of 0.9 % physiological solution, n=10), groups 2 and 4 – intracerebral RAIL administration at doses of 10 μg and 20 μg (n=10 each), groups 3 and 5 – combined administration of RAIL in both doses and LVT (n=10 each).

Human RAIL was administered i.p. and intracerebrally. With this aim animals were anesthetized with pentobarbital sodium ("Seva", i.p., 30 mg/kg) and the stainless steel guide cannulas (ext. diameter 0.6 mm) were implanted stereotaxically into the left lateral brain ventricle (icv; AP=0.8; L=1.5; H = 3.5), bilaterally into the reticular part of substantia nigra (inig; AP=-5.3; L=2.5; H=8.0) or the CA1 hippocampi (ihip; AP=-4.8; L=4.5; H=8.0) according to the rat brain atlas (Photographic Atlas of the Rat Brain the Cell

and Fiber Architecture Illustrated in Three Planes With Stereotaxic Coordinates: A Photographic Guide to the Cell and Fiber Architecture of the Rat Brain Illustrated in Three Planes With Stereotaxic Coordinates. Kruger L, 1995). Cannulas were fixed to the skull by acrylic cement (SPOFA). The postoperative period was 7–10 days, during which, to avoid cannula replacement, rats were housed individually in plexiglass chambers measuring 15 cm x 15 cm x 25 cm with holes for air intake.

The rats, after convulsant injections, were placed in individual transparent plastic chambers (10 cm x 25 cm x 30 cm), and the severity of convulsive reactions was evaluated according to "blinding scoring" using a 6-point scale [13]. The number of rats with generalized clonic-tonic seizures was also counted, and the latency of the first convulsive reaction was estimated. The epoch of observation was 60 min after PTX administration and 10 min after PTZ and KA administrations.

There were no episodes of rat mortality after convulsant administration, during either kindling or postkindling induction.

After the end of the trials, the animals were sacrificed by pentobarbital sodium overdose (i.p., 100 mg/kg), and the sites of intracerebral microinjections were verified histologically by comparing the injection sites with the atlas figures. Only cases with the cannulas appropriately positioned at the injection sites were considered for further analysis.

The power analysis conducted before the start of the experimental trial enabled the determination of a sufficient sample size for adequate statistics and convincing results. The data were analyzed statistically using the parametric Bonferroni test for interval-scale data (seizure latency) and the nonparametric Kruskal-Wallis test for ordinal-scale data (seizure severity and the number of rats with a specific type of seizure manifestation). $p<0.05$ was accepted as the index of significant differences.

Results of the study and their discussion. Picrotoxin-induced seizures were characterized by generalized clonic-tonic seizures development with falling and postseizure depression in 9 out of 10 rats; such seizures were recorded repeatedly in 3 animals (Table 1). After RAIL administration at maximal dose, the intensity of picrotoxin-induced generalized convulsive reactions was less compared with the same control index ($p<0.01$). At the same time, generalized clonic-tonic seizures developed in only 2 of 10 rats, and clonic facial and forelimb twitching was observed in 5 rats (in both cases, $p<0.05$). The first convulsive reaction latency was 83 % longer than in intact rats ($p<0.01$). Comparable indexes of convulsive reactions were observed during simultaneous administration of RAIL and LVT.

Table 1

Levetiracetam impact on the intensity of acute generalized seizures in rats after RAIL systemic administration

Experimental groups, number of rats	Number of rats with seizures intensity						P, vs control	Latency M±m, min
	0	1	2	3	4	5		
Picrotoxin-induced seizures								
PCT + saline, n=10	0	0	0	1	6	3	-	10.6±1.4
Saline + LVT, n=12	0	4	3	5	0	0	<0.05	15.4±1.6*
PCT + RAIL (7,5 mg/kg), n=12	0	0	1	7	3	1	>0.05	17.6±1.6*
PCT + RAIL + LVT, n=12	0	4	4	4	0	0	<0.05	16.3±1.7*
PCT + RAIL (10 mg/kg), n=12	0	3	5#	2	2#	0	<0.01	19.4±1.8*
PCT + RAIL + LVT, n=12	0	4	5#	2	1#	0	<0.01	18.7±1.7*
Pentylenetetrazole-induced seizures								
PTZ + saline, n=10	0	0	0	2	6	2	-	1.6±0.2
Saline + LVT, n=12	0	0	3	6	3	0	<0.05	3.6±0.4*
PTZ + RAIL (7,5 mg/kg), n=12	0	0	2	6#	4	0	<0.05	3.2±0.3*
PTZ + RAIL + LVT, n=12	0	3	4#	3	2	0	<0.05	3.9±0.4*
PTZ + RAIL (10 mg/kg), n=12	0	3	4#	3	2#	0	<0.05	3.6±0.3*
PTZ + RAIL + LVT, n=12	0	5#	5#	2	0#	0	<0.01[1]	4.9±0.4*[2]
Kainic acid-induced seizures								
KA + saline, n=10	0	0	0	0	4	6	-	7.9±0.7
Saline + LVT, n=12	0	0	1	6#	4	1#	>0.05	12.2±1.4
KA + RAIL (7,5 mg/kg), n=12	0	0	0	3	6	3	>0.05	11.6±1.2
KA + RAIL + LVT, n=12	0	0	1	5#	5	1#	>0.05	13.1±1.3
KA + RAIL (10 mg/kg), n=12	0	0	0	6#	5	1#	>0.05	13.6±1.5*
KA + RAIL + LVT, n=12	0	1	6#	3	2#	0#	<0.01[1]	17.3±1.6*[2]

Notes: * – $p<0.05$ – statistical differences of the investigated indexes compared with the same in corresponding control group (Bonferroni criterion); # – $p<0.05$ – statistical differences of the investigated indexes compared with the same in corresponding control group (Kruscal-Wallis criterion); 1 – $p<0.05$ – statistical differences of the investigated index compared with the same in the group without LVT administration (Bonferroni criterion); 2 – $p<0.05$ – statistical differences of the investigated index compared with the same in the group without LVT administration (Kruscal-Wallis criterion).

The first generalized PTZ-induced convulsions latency was 1.6±0.2 min. Generalized clonic-tonic convulsions in these conditions developed in 80 % of animals. When RAIL was administered, the latency to the first convulsion was significantly prolonged (by 2 times and 2.25 times, respectively). Their intensity was

lower than the control values due to a decrease in the number of rats with generalized clonic-tonic convulsions and an increase in the number of rats with clonic facial and forelimb twitching (in all cases, p<0.05). When RAIL was co-administered with LVT, the facial muscles' small twitches and forelimbs' clonic contractions were recorded in 10 rats (p<0.05), the intensity of seizure reactions was significantly less compared to the control rats (p<0.01), and with a similar index in rats with RAIL injection (p<0.05). The first convulsive reaction latency was 3.1 times higher than the corresponding index in intact rats and 36.1 % longer than in rats after RAIL administration (in all cases, p<0.05).

RAIL was unable to control seizure manifestations in conditions of kainic acid-induced acute generalized seizures. Tremor of vibrissae and facial muscles, as well as forelimbs, and clonic contractions were registered in 8 rats after RAIL and LVT combined administration. At the same time, the intensity of kainate-induced seizures was lower than in these control groups (p<0.01) and in rats receiving RAIL (p<0.05). The first seizure reaction latency in these conditions was significantly longer than the analogous indexes in control group rats and in rats with RAIL administration (by 2.2 times and by 27.1 %, respectively; p<0.05 in both cases).

Seizures in 100 % of rats with ready kindling were characterized by generalized convulsive clonic-tonic seizures with falling and postseizure depression; these reactions developed repeatedly in 3 rats (Table 2).

Table 2

Levetiracetam impact on chronic seizure intensity in rats after RAIL intracerebral administration

Experimental groups, number of rats	Number of rats with seizures intensity						P, vs control	Latency M±m, min
	0	1	2	3	4	5		
Kindling								
Saline, n=10	0	0	0	0	7	3	-	13.8±1.4
RAIL (icv, 10 μr), n=10	0	0	3	3	4	0	<0.05	24.6±2.4*
RAIL + LVT, n=10	0	0	1	3	5	1	<0.05	18.3±1.6*
RAIL (icv, 20 μr), n=10	0	0	5#	4	1#	0	<0.01	29.8±2.7*
RAIL + LVT, n=10	0	0	6	4	0	0	<0.01	27.9±2.8*
RAIL (inig, 10 μr), n=10	0	0	0	1	6	3	>0.05	16.6±1.6
RAIL + LVT, n=10	0	0	0	4	4	2	>0.05	18.7±1.8*
RAIL (inig, 20 μr), n=10	0	0	1	4	4	1	<0.05	17.4±1.8
RAIL + LVT, n=10	0	0	2	3	4	1	<0.05	20.3±2.1*
RAIL (ihip, 10 μr), n=10	0	0	0	3	7	0	>0.05	17.9±1.8
RAIL + LVT, n=10	0	0	1	3	6	0	>0.05	19.4±2.1*
RAIL (ihip, 20 μr), n=10	0	0	3	5#	2#	0	<0.05	22.7±2.1*
RAIL + LVT, n=10	0	3	4	3	0#	0	<0.05@	32.4±2.3*@
Postkindling								
Saline, n=10	0	0	0	0	5	5	-	14.6±1.4
RAIL (icv, 10 μr), n=10	0	0	3	4	3	0#	<0.05	25.6±2.4*
RAIL + LVT, n=10	0	0	4	5#	1	0#	<0.05	27.1±2.3*
RAIL (icv, 20 μr), n=10	0	0	5#	4	1	0#	<0.05	30.8±2.8*
RAIL + LVT, n=10	0	2	4	4	0	0#	<0.05	31.6±2.7*
RAIL (inig, 10 μr), n=10	0	0	0	1	5	4	>0.05	16.3±1.6
RAIL + LVT, n=10	0	0	0	4	5	1	>0.05	17.1±1.8
RAIL (inig, 20 μr), n=10	0	0	4	3	3	0#	<0.05	16.8±1.6
RAIL + LVT, n=10	0	1	3	6#	0	0#	<0.05	27.1±2.4*@
RAIL (ihip, 10 μr), n=10	0	0	0	2	7	1	>0.05	17.1±1.6
RAIL + LVT, n=10	0	0	0	5#	5	0#	>0.05	17.8±1.7
RAIL (ihip, 20 μr), n=10	0	0	2	5#	3	0	<0.05	21.9±2.3*
RAIL + LVT, n=10	0	4	5	1	0	0	<0.01@	30.8±2.4*@

Notes: * – p<0.05 – statistical differences of the investigated indexes compared with the same in corresponding control group (Bonferroni criterion); # – p<0.05 – statistical differences of the investigated indexes compared with the same in corresponding control group (Kruscal-Wallis criterion); 1 – p<0.05 – statistical differences of the investigated index compared with the same in the group without LVT administration (Bonferroni criterion); 2 – p<0.05 – statistical differences of the investigated index compared with the same in the group without LVT administration (Kruscal-Wallis criterion).

The studied indices of convulsive reactions after RAIL, when administered intraventricularly, differed significantly from those in the control group (p<0.05) and were comparable across all groups.

We obtained analogous results in animals with separate intranigral administration of RAIL at the maximal dose and with LVT.

All rats demonstrated facial muscle twitching and clonic contractions of the trunk and forelimbs after RAIL intrahippocampal administration at the maximal dose, in addition to LVT. The intensity of the seizure reactions was lower for the same index in the control group and in rats with RAIL injection (in both cases, p<0.05). The first convulsions latency significantly exceeded the same control index (by 2.3 times) and the corresponding index in rats after RAIL injection (by 42.7 %; in both cases, p<0.05).

Seizure indexes in rats of all groups in the postkindling stage after RAIL icv administration were significantly different from the analogous control rates (p<0.05).

Generalized seizure reactions were absent in rats after RAIL intranigral administration with LVT; the intensity of seizures was lower than in the control ($p<0.05$). The first seizures in rats in these conditions occurred 85.6 % later than in control observations and 61.3 % later than in rats with RAIL administration (in both cases, $p<0.05$).

In rats at the postkindling stage, intranigral RAIL administration, together with LVT, contributed to protection against generalized clonic-tonic convulsive reactions and a considerable increase in the number of rats with clonic twitching of facial and forelimb muscles. Seizure reactions' intensity and latency significantly differed from the same indexes in intact rats and in postkindled rats with RAIL injection (in all cases, $p<0.05$).

Thus, the data obtained allowed the identification of a leading principal result: the animals' protection from acute generalized and chronic seizures during the kindling and post-kindling stages under IL-1 receptor blockade. Another principal result we consider is the enhancement of RAIL anticonvulsant efficacy with combined LVT injections.

Our intermediate conclusions are the following. Firstly, we observed that animals' protection from seizure reactions due to interleukin receptor activity block occurs following RAIL administration, both systemic and intracerebral.

Secondly, it was demonstrated that LVT administration enhanced RAIL anticonvulsant efficacy in PTZ- and kainic acid-induced acute generalized convulsive reactions. Both RAIL and LVT injection efficacy was manifested by a significant decrease in seizure reaction intensity, protection of animals from generalized convulsive reactions, including repeated ones, and prolongation of the first seizure latency.

Thirdly, the severity of kindling and postkindling chronic convulsive reactions is significantly alleviated in the case of RAIL intrahippocampal administration together with LVT. RAIL intranigral administration together with LVT enhanced the interleukin receptor block anticonvulsant effect only during the postkindling stage.

Fourthly, the analysis of the obtained results, with a focus on the mechanisms of anticonvulsant efficacy after RAIL administration, indicates that the inflammatory reaction is involved in the pathogenetic mechanisms of the convulsive syndrome.

With the aim of discussion, we consider it appropriate to highlight the following: the first one. In a model of acute generalized seizures, we observed enhanced anticonvulsant effects of RAIL and LVT only when PTZ and KA induced seizures. Understanding the mechanisms underlying these convulsants' efficacy suggests a more pronounced LVT-potentiating effect when IL–1 receptor activity is blocked, driven by increased excitatory amino acid activity and decreased GABAergic inhibition.

The second. RAIL intracerebral administration together with LVT was mainly effective in terms of the most expressed antiserizure efficacy in case of intrahippocampal and intranigral (in postkindling) block of IL–1 receptor activity. We consider this interesting from the following perspectives: the hippocampus is considered a determinant of the seizure syndrome, and the ventral hippocampus belongs to the so-called proconvulsant functional system [3, 9].

Thirdly, the data on the LVT anticonvulsant mechanism of action are interesting, as they address the pharmacodynamic interaction between LVT activity and interleukin receptor blockade. Important that LVT binds to the SV2A protein, which is an integral membrane protein with predominantly synaptic localization [6]. The SV2 isoforms are expressed primarily in the thalamus, basal ganglia, and hippocampus [12], which, to some extent, explains the anticonvulsive effect we observed after RAIL intracerebral injections and combined administration with LVT.

LVT was shown to exhibit anticonvulsant, neuroprotective, and analgesic efficacy, with mechanisms associated with SV2A protein interaction, inhibition of both Ca2+ and Na+ channels, and modulation of the GABA, serotonin, α2-adrenergic, and μ-opioid neurotransmitter systems [4]. The IL–1 receptor block under the influence of LVT antiseizure effect enhancement corresponds to data devoted to the relief of focal, febrile, and post-traumatic seizures by this drug [4].

Fourthly, the inflammatory process's pathogenetic contribution to epileptogenesis is essential. We emphasize this, since, traditionally, the pathogenetic mechanisms of the convulsive syndrome were considered to be an inhibitory GABA-ergic neurotransmission compromise and excitatory amino acid overactivation [3]. Our data emphasize an essential idea of the potential anticonvulsant efficacy in the case of receptor apparatus block, which ensures the formation of the “interleukin-1-beta – binding receptor” complex. Hence, the involvement of the inflammatory syndrome, which is traditionally indifferent to the process of seizure initiation and the excessive bioelectrical activity spread throughout the brain, in the pathogenetic mechanisms of epileptogenesis is apparent.

A mesmerizing question, we suppose, is the following: Is inflammation primary or secondary to the onset of a convulsive reaction? Inflammation, according to fundamental ideas, is well known to be a consequence of extreme brain catastrophes, i.e., traumatic and ischemic brain damage, neuroinfection, chronic convulsive syndrome, etc. In other words, inflammation, being a consequence of convulsive syndrome, due to cause-and-effect relationships mechanisms and to “vicious circle” formation with nervous,

immune, and humoral systems pathological dysregulation, also acts as an etiological factor of chronic convulsive syndrome or a trigger for seizure reactions intensity increase [2, 8, 14]. An essential strategy for developing promising anticonvulsant therapy regimens is the additional use of cytokine synthesis inhibitors and inhibitors of cytokine binding to their receptors. We believe this approach to pharmacotherapeutic strategies is hopeful for patients with seizures resistant to traditional antiepileptic drugs.

Thus, we are talking about the comprehensive regimen for convulsive syndrome pathogenetically based therapy development, which combines the efficacy of a traditional anticonvulsant drug and interleukin receptor activity block.

In summary, this is a fundamental opportunity to increase the efficacy of anticonvulsant strategies in a complex group of epilepsy patients resistant to traditional treatments by combining pharmacological agents that block neurotransmitter systems responsible for initiating and propagating hyperactive brain activity, and that provide anti-inflammatory effects.

Conclusions

1. Interleukin receptor activity block by recombinant antagonist of interleukin receptor administration helps to protect animals from acute generalized and chronic seizures during kindling and postkindling.

2. Recombinant antagonist of interleukin receptor systemic and intracerebral administration anticonvulsant efficacy manifested by seizure reactions intensity significant reduction, animals' protection from generalized convulsive reactions, including repeated ones, as well as the first convulsions latency prolongation is enhanced by levetiracetam.

3. The revealed anticonvulsant effect is realized in acute generalized pentylenetrazole and kainic acid-induced seizures as well as in chronic convulsive syndrome in conditions of intra-hippocampal block of interleukin receptors.

4. The obtained results indicate the involvement of the inflammatory response in the pathogenetic mechanisms of seizure syndrome.

5. In the experiment, a fundamental possibility of an anticonvulsant strategy efficacy increases in patients with epilepsy resistant to traditional treatment was achieved by co-administration of pharmacological drugs that block the activity of neurotransmitter systems responsible for excessive bioelectrical activity initiation and propagation.

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