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SGLT-2 INHIBITORS AS POTENTIAL ANTICONVULSANTS: EMPAGLIFLOZIN, BUT NOT DAPAGLIFLOZIN, RENDERS A PRONOUNCED EFFECT AND POTENTIATES THE SODIUM VALPROATE ACTIVITY IN PENTYLENETETRAZOLE-INDUCED SEIZURES

Vadim Tsyvunin, Sergiy Shtrygol', Ihnat Havrylov, Diana Shtrygol', Artur Reus

On the way to the search for effective adjuvant medicines for epilepsy treatment, antidiabetic medicines such as sodium-glucose cotransporter-2 inhibitors, which are expressed not only in the kidneys but also in the brain, attract attention. From previous studies, it is known that dapagliflozin improves electroencephalographic parameters in rats on the model of pentylenetetrazole-induced seizures. However, the anticonvulsant potential of other medicines from this group needs to be clarified.

The aim of the study *is to estimate the effect of empagliflozin, dapagliflozin per se and their combinations with sodium valproate on pentylenetetrazole-induced seizures, as well as on muscle tone and motor coordination in mice.*

Material and methods. *42 random-bred male albino mice weighing 24-28 g were used in the experiments. Empagliflozin (20 mg/kg) and dapagliflozin (50 mg/kg) were administered intragastrically for 3 days. The classic anticonvulsant sodium valproate (150 mg/kg) per se, in combination with the medicines mentioned above, was administered in a similar regimen. On the second day, 30 minutes after administering all medicines, their effect on muscle tone and coordination of movements was determined in the rotarod test. On the third day, 30 minutes after the last administration of the medicines, their effect on pentylenetetrazole-induced (80 mg/kg subcutaneously) seizures was studied.*

Results. *For the first time, a pronounced anticonvulsant effect of empagliflozin was established both when used alone (a significant increase in latency of the convulsions and a decrease in lethality by 43 %) and especially in combination with sodium valproate (a significant increase in latency of the convulsions, a decrease in the number and severity of seizures and a decrease in lethality by 83 %), as well as the absence of a muscle relaxant effect in both cases. Dapagliflozin has neither its anticonvulsant properties nor its effect on the action of sodium valproate. However, this medicine caused muscle relaxation, especially when combined with sodium valproate.*

Conclusions. *The results suggest that empagliflozin, unlike dapagliflozin, has a high potential as an adjuvant medicine in treating epilepsy, as it enhances the efficacy of the classic anticonvulsant sodium valproate without muscle relaxant side effects*

Keywords: *anti-epileptic medicines, adjuvants, inhibitors of SGLT-2, chemo-induced seizures, mice*

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1. Introduction

Epilepsy is a severe chronic disease that occupies one of the first places in the general structure of disorders of the central nervous system. It has adverse cognitive, psychological and social consequences and significantly impairs the quality of life. According to the World Health Organization, more than 50 million people suffer from epilepsy, about 1 % of the planet's total population (WHO, 2021) [1]. Epilepsy requires long-term, often even lifelong, treatment. Unfortunately, about 25 % of patients are multidrug-resistant, and even treatment with 3–4 anti-epileptic medicines (AEDs) does not allow seizure control and condition relief [2, 3]. Furthermore, polypharmacy significantly increases the severity of AEDs' side effects and accelerates medicine addiction development, further complicating treatment. In addition, AEDs often cause side effects [4].

Therefore, the search for original anticonvulsant medicines and the development of ways to increase the effectiveness of known AEDs is an urgent problem. The use of non-antiepileptic medicines as adjuvant agents, which have anticonvulsant properties and enhance the effects of classical AEDs, is gaining more comprehensive application. Such medicines include, in particular, non-steroidal anti-inflammatory medicines, sodium channel blockers (in particular, lidocaine), slow calcium channel blockers, β-blockers, the If-channel blocker ivabradine, the competitive xanthine oxidase inhibitor allopurinol, statins, selective phosphodiesterase-5 inhibitors (sildenafil, tadalafil), the cardiac glycoside digoxin [5–18].

Attention is drawn to the polymodal properties of a new class of antidiabetic medicines – the sodium-glucose transport protein 2 (SGLT-2) inhibitors, which suppress the reabsorption of glucose in the tubules of the kidneys [19]. SGLT-2 inhibitors are a class of modern medications used to lower blood glucose levels in adults with type 2 diabetes. This group includes canagliflozin, dapagliflozin and empagliflozin. SGLT-2 inhibitors are

interesting for their advantages over other antidiabetic medicines, including lowering HbA1c, body weight, and blood pressure. In addition, these medicines reduce the risk of serious cardiovascular events and slow the progression of diabetic chronic kidney disease [20, 21].

SGLT-2 is expressed not only in the kidney but also in the brain, especially in the cerebellum, hippocampus, frontal cortex, caudate nucleus, striatum, amygdala, parietal cortex, and paraventricular nucleus of the hypothalamus [22]. SGLT-2 is involved in the transmembrane transport of Na^+ ions and therefore affects the subtle mechanisms of membrane excitability. The impact on this target is not inherent in the known AEDs. Given the multifunctional role of SGLT-2, including the regulation of membrane potentials and neuronal metabolism [23], it can be assumed that the therapeutic potential of selective SGLT-2 inhibitors has not yet been fully explored. Therefore, it is reasonable to investigate the effect of SGLT-2 blockers on seizures.

There are few publications on this issue. Non-selective SGLT-1 and SGLT-2 inhibitor phlorizin demonstrated the ability to prevent seizures in the pilocarpine-induced status epilepticus model [24]. Inhibition of SGLT contributed to the reduction of neurodegeneration in some brain areas after 15 days of experimental seizures.

Another study revealed anticonvulsant properties in the PTZ-induced seizure model of a more specific antidiabetic medicine, the selective SGLT-2 inhibitor dapagliflozin, at high doses of 75 and 150 mg/kg in rats [25]. The positive effect was established by reducing the percentage of spike waves on the electroencephalogram and improving the time to the first myoclonic jerk. The authors explain the anticonvulsant effect by reducing the cerebral availability of glucose and reducing the transport of Na^+ ions through the membranes of neurons, which can stabilize them, and emphasize the potential value of dapagliflozin and other SGLT-2 inhibitors as anticonvulsant medicines should be further investigated.

The possibility of treating super refractory status epilepticus using a ketogenic diet (KD) in combination with dapagliflozin has been demonstrated [26]. The KD is characterized by a high-fat content, low carbohydrate content and a sufficient amount of protein, which simulates a state of starvation, provoking the metabolism of fats for the production of energy and ketone bodies. A wide range of evidence suggests that the KD can be effective in treating epilepsy [27]. SGLT-2 inhibitors (ipragliflozin, dapagliflozin, luseogliflozin, tofogliflozin, canagliflozin, and empagliflozin) promote a metabolic shift toward lipolysis and ketogenesis in the liver, causing ketoacidosis, which is often euglycemic [28] and has been used in a clinical trial [26]. A patient who could not maintain ketosis only on the KD, using the SGLT-2 inhibitor, can achieve stable ketosis, which helped to overcome super-refractory epileptic status [26].

Therefore, the study of the effect of SGLT-2 inhibitors on seizure syndrome is a promising direction that can offer new methods of epilepsy treatment, including medicine-resistant ones. The question arises of the presence of anticonvulsant properties in other medicines of this group (including empagliflozin), their influence on the severity of the anticonvulsant effect of classical AEDs, optimal combinations of SGLT-2 inhibitors with classical AEDs, dose regimen, interaction mechanisms.

Thus, the aim of this work is to find out the comparative effect of SGLT-2 inhibitors dapagliflozin and empagliflozin on the basic model of pentylenetetrazol (PTZ)-induced seizures in mice as well as to determine the effect of these medicines on muscle tone and coordination of movements.

2. Planning (methodology) of the research

The methodology was designed as follows in Fig. 1.

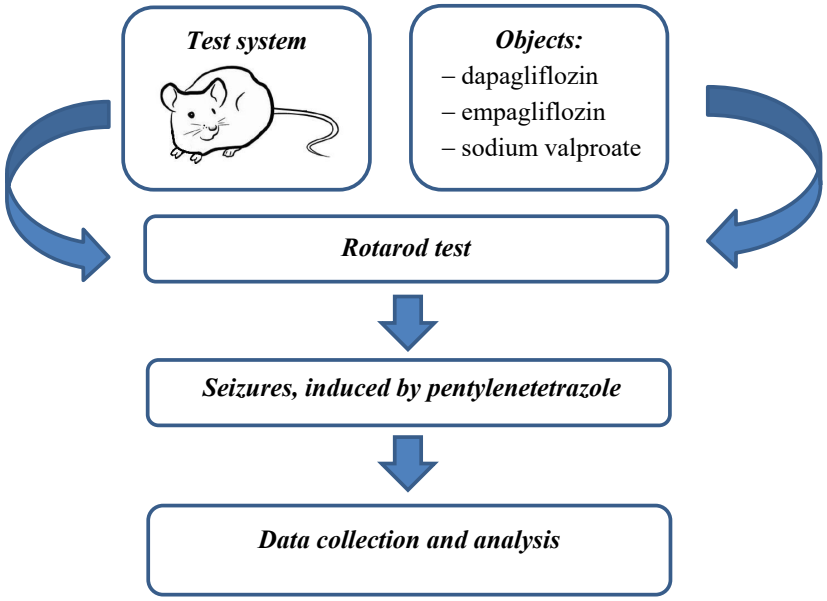

Fig. 1. Algorithm of the research

The research was performed using mice as a convenient universal test system to study the anticonvulsant effect of medicines [29]. Pentylenetetrazole-induced seizures were used. The studied medicines were administered once daily for 3 days. After the 2nd administration, movement coordination and muscle tone were checked in the rotarod test [30, 31], and after the final 3rd administration, convulsions were simulated.

3. Material and methods

The study was carried out in the autumn season of 2021. The experiments were conducted on 42 random-bred male albino mice weighing 24–28 g following the principles and requirements of the EU Council Directive (2010) on the protection of animals used for scientific purposes as well as the current Procedure for carrying out experiments on animals by scientific institutions,

approved by Order of the Ministry of Education and Science, Youth and Sports of Ukraine No. 249 (2012). Mice were kept on a standard diet in a vivarium with free access to food and water, constant humidity, a 12-hour light/dark cycle, and a temperature of +18–20 °C at the Central Research Laboratory of the Educational and Scientific Institute of Applied Pharmacy of the National University of Pharmacy. The experiment was approved by the Committee of bioethics of the National University of Pharmacy (protocol No. 3, September 10, 2020).

The animals were randomly divided into the following groups of 6–7 mice each: 1 – seizure control; 2 – sodium valproate; 3 – dapagliflozin; 4 – dapagliflozin + sodium valproate; 5 – empagliflozin; 6 – empagliflozin + sodium valproate.

The studied medicines dapagliflozin (Forxiga, AstraZeneca, Great Britain) and empagliflozin (Jardins, Boehringer Ingelheim Pharma, Germany) in the form of stabilized by Tween-80 aqueous suspensions were administered in a prophylactic mode consecutively for 3 days intragastrically (i.g.) at the doses of 50 mg/kg and 20 mg/kg respectively in an appropriate volume of 0.1 ml per 10 g of body weight, the last time – 30 minutes before the start of the experiments. When choosing the dose of dapagliflozin, we were guided by the data [25]; however, seeing that the dose in the cited study was extremely high, it was considered appropriate to reduce it by 1/3. The dose of empagliflozin was chosen based on the ratio of adequate doses of this medicine in diabetology. Sodium valproate (Depakine, Sanofi Aventis, France) is a ready-made syrup at a dose of 150 mg/kg [15], which is not maximally effective and equals 1/2 ED_{50}, which allows for detecting both enhancement and attenuation of the anticonvulsant effect. To study the effect of medicine combinations, each SGLT-2 inhibitor and sodium valproate were administered, i.g. in the same doses as per se (empagliflozin 20 mg/kg, dapagliflozin 50 mg/kg, sodium valproate 150 mg/kg) with an interval of 7–10 minutes. There is no information on the pharmacokinetic interaction of both SGLT-2 inhibitors with valproate. Control animals received purified water.

To determine the potential neurotoxic effect of empagliflozin, dapagliflozin and their combinations with sodium valproate, the effect of the medicines on muscle tone and coordination of movements of mice in the rotarod test [30, 31] was previously investigated. The device is a horizontal cylinder with a diameter of 2 cm, which rotates around its axis with the help of an electric motor at a constant speed of 10 revolutions per minute. The number of animals that fell from the rod before the 30^{ty} second, 1st, 3rd, and 5th minutes was determined.

The anticonvulsant properties of empagliflozin, dapagliflozin and their combinations with the classic AED sodium valproate were determined in the basic model of seizures induced by PTZ [31]. PTZ (Sigma, USA) in the form of an aqueous solution at a dose of 80 mg/kg was administered to animals subcutaneously. Immediately after administering the convulsant, the animals were placed in separate transparent plastic cylindrical boxes with a volume of 5 L and continuously observed for 60 min.

The expressiveness of the anticonvulsant effect of the medicines and their combinations was evaluated according to the following indicators: latency, number of clonic-tonic paroxysms per 1 mouse, % of animals in the group separately with clonic and tonic seizures, seizure severity in points: 1 – trembling; 2 – circus movement; 3 – clonic seizures; 4 – clonic-tonic seizures with a lateral position; 5 – tonic extension; and 6 – tonic extension leading to the animal's death, duration of the convulsive period, the lifetime of animals until death and lethality [15]. For example, if convulsions did not occur for 1 h, then the latency period would equal 60 min.

For statistical analysis, STATISTICA 12.0 software for Windows was used. The results are expressed as mean ± standard error of the mean (Mean ± SEM). The level of statistical significance was considered as $p<0.05$. Statistical differences between groups were analyzed using the Mann-Whitney U test. When accounting for the results in an alternative form (% of animals that fell from the rod in certain time intervals, % of mice with clonic and tonic convulsions, lethality), the Fisher's angular transformation was used [32].

4. Results

The results of the effect of SGLT-2 inhibitors *per se* and in combinations with sodium valproate on muscle tone and coordination of movements of mice are shown in Table 1.

Table 1

Effect of dapagliflozin, empagliflozin and their combinations with sodium valproate on muscle tone and coordination of movements of mice in the rotarod test

Group of animals	Fallen animals			
	before 30^{ty} sec	before 1st min	before 3rd min	before 5th min
Control (n=6)	1 (17 %)	2 (33 %)	4 (67 %)	4 (67 %)
Sodium valproate, 150 mg/kg (n=6)	2 (33 %)	3 (50 %)	4 (67 %)	5 (83 %)
Dapagliflozin, 50 mg/kg (n=7)	3 (43 %)	4 (57 %)	5 (71 %)	7* (100 %)
Dapagliflozin + sodium valproate (n=7)	4 (57 %)	6* (86 %)	7*$^{\#}$ (100 %)	7* (100 %)
Empagliflozin, 20 mg/kg (n=7)	0$^{\#\wedge\wedge}$ (0 %)	2 (29 %)	3 (43 %)	4$^{\wedge\wedge}$ (57 %)
Empagliflozin + sodium valproate (n=6)	1 (17 %)	1$^{\&\&}$ (17 %)	4$^{\&}$ (67 %)	5 (83 %)

*Note: n – number of animals in each group. * – p<0.05 compared with control; # – p<0.05 compared with sodium valproate; ^^ – p<0.01 compared with dapagliflozin; & – p<0.05, && – p<0.01 compared with combination dapagliflozin + sodium valproate.*

In the rotarod test, sodium valproate tended to worsen the coordination of movements, but the differences with the control did not reach statistical significance. Dapagliflozin for each measurement control point increased the number of mice that fell down the rod, and by the 5th minute, it was 100 %, which is significantly higher than the control value ($p<0.05$). The combination of dapagliflozin with sodium valproate had the worst test results: already within the first minute, 86 % of mice fell down the rod, which is 53 % more than in the control group ($p<0.05$), while none of the animals stayed on the rod for 3 minutes ($p<0.05$ for control and sodium valproate *per se*). Thus, dapagliflozin significantly worsens muscle tone and coordination of movements and also potentiates the corresponding effect of sodium valproate.

There have been no adverse effects of empagliflozin and its combination with sodium valproate on skeletal muscle tone and movement coordination. This was determined due to the absence of statistically significant differences in the number of mice that fell from the rod before the 30ty second, the 1st, the 3rd and the 5th minutes regarding control. Furthermore, empagliflozin even statistically significantly reduces the % of animals that fell from the rod before the 30ty second, compared to sodium valproate ($p<0.05$) and dapagliflozin ($p<0.01$). In addition, empagliflozin, in contrast to dapagliflozin, reduces the impairment of muscle tone and coordination of movements caused by sodium valproate: the number of mice that fell off the rod compared to the combination of empagliflozin + sodium valproate was less than the combination of dapagliflozin + sodium valproate throughout the experiment, and at the 1st minute and the 3rd minute time points, these differences were statistically significant ($p<0.01$ and $p<0.05$, respectively). These results indicate that empagliflozin has no neurotoxic properties in motor coordination and no adverse interaction with sodium valproate.

After the third administration of the medicines, within 15–20 minutes, a marked deterioration in motor activity and depression of consciousness was observed in mice treated with dapagliflozin *per se* and in combination with sodium valproate. In the next 10–15 minutes, 1 animal out of 7 died when dapagliflozin was administered, and 3 animals out of 7 when dapagliflozin was administered together with sodium valproate. The following experiments were carried out in the surviving mice.

The results of the study of the effect of SGLT-2 inhibitors *per se* and in combination with sodium valproate on the PTZ-induced seizures in mice are shown in Table 2. In the control group, PTZ induced a severe convulsive syndrome. The tonic extension has been developed in all mice, which caused 100 % lethality. The reference medicine sodium valproate exerted a typical anticonvulsant effect, manifested by a statistically significant increase in the latency, a decrease in tonic and clonic seizures in 1 animal, and a two-fold decrease in lethality to 50 % ($p<0.01$).

Dapagliflozin had almost no effect on the seizures, only tending to prolong the latency by 2.18 times, reduce the convulsions by 1.46 times, the duration of seizures by 1.63 times, and the lethality from 100 % to 83 %, which was not statistically significant. Furthermore, the protective effect of sodium valproate was weakened by dapagliflozin: any indicator of the seizure course was not significantly different from the control, all animals had both clonic and tonic seizures, and the lethality was 75 %.

Empagliflozin has inherent anticonvulsant properties, which were verified by a pronounced statistically significant increase in the latency by 5.9 times compared to the control, as well as by a probable decrease in animal lethality (by 43 % compared to a similar indicator of a group of animals with untreated seizures, $p<0.01$). In addition, empagliflozin tends to reduce the severity of attacks and the duration of the seizure period.

Table 2

Anticonvulsant effect of dapagliflozin, empagliflozin and their combinations with sodium valproate in the PTZ-induced seizures in mice

Group of animals	Latency, min	Number of clonic-tonic seizures in 1 mouse	% of mice with convulsions		The severity of seizures, points	Period of seizures, min	Time to death, min	Lethality, %
			clonic	tonic				
Control – untreated seizures (n=6)	2.35±0.46	3.17±0.48	100	100	6.00±0.00	10.74±2.36	13.09±2.55	100
Sodium valproate (n=6)	23.47±11.57**	2.33±0.92	67*	67*	3.83±1.22	8.76±4.67	13.09±4.68	50**
Dapagliflozin (n=6)	5.13±1.75#	2.17±0.48	100	100	5.67±0.33	6.55±2.24	13.14±2.53	83
Dapagliflozin + sodium valproate (n=4)	19.23±13.75	2.25±0.85	75	75	4.50±1.50	5.17±4.08	12.53±4.52	75
Empagliflozin (n=7)	13.75±7.82*	2.57±0.90	86	86	4.71±0.84	7.26±4.48	10.69±1.68	57**
Empagliflozin + sodium valproate (n=6)	10.69±2.39**	1.67±0.33*	100	83	4.33±0.42*	5.52±2.62	17.00±2.89	17**#

*Note: n – number of animals in each group; PTZ – pentylenetetrazole. * – $p<0.05$, ** – $p<0.01$ compared with control; # – $p<0.05$ compared with valproate.*

The combination of empagliflozin with sodium valproate has a distinct anticonvulsant effect: it significantly prolongs the latency period of convulsions relative to the control (by 4.5 times, $p<0.01$), halving the number of clonic-tonic attacks in 1 mouse ($p<0.05$) and reducing the severity of paroxysms by almost one and a half times. Also, the combination of medicines almost halves the duration of the convulsive period. However, due to the high dispersion of the indicator, this difference does not reach the level of statistical significance. In terms of the effect on the main integral indicator of effectiveness – the lethality of animals – the combination of empagliflozin with sodium valproate is not only statistically significantly different from the control (17 % vs 100 %, $p<0.01$) but also probably exceeds the effect of sodium valproate *per se* (17 % vs 50 %, $p<0.05$).

The obtained results give reason to believe that empagliflozin exhibits its anticonvulsant properties and enhances the anticonvulsant potential of a low dose of the classic AED sodium valproate while not having neurotoxic effects on locomotor activity.

5. Discussion

The results of our comparative study of the effects of dapagliflozin, empagliflozin and their combinations with sodium valproate on muscle tone and coordination of movements of animals in the rotarod test demonstrate the contrasting properties of different SGLT-2 inhibitors. Thus, dapagliflozin and its combination with sodium valproate already in the first 30 seconds caused incoordination of animal movements. Almost all mice fell from the rod before the 3rd minute, and by the 5th minute, none of them lasted. On the contrary, the animals under empagliflozin and its combinations with sodium valproate at the beginning of the experiment demonstrated the ability to stay on the rod much better than in the control and reference medicine groups.

As a result, empagliflozin and its combination with sodium valproate did not affect the muscle tone and coordination of the animals in the test. These results are consistent with the data [33] that exercise endurance capacity was limited in the heart failure mice but was ameliorated in empagliflozin-treated mice without any effects on spontaneous physical activity and skeletal muscle strength.

Therefore, a significant deterioration in the coordination of animal movements when using dapagliflozin *per se* and especially when combined with sodium valproate, may indicate its neurotoxicity. Perhaps such an effect is due to the chosen dose of 50 mg/kg, which requires studying the dose dependence of the effect, especially since the study [34] revealed an antiparkinsonian effect of dapagliflozin at a significantly (by order of magnitude) smaller dose of 1 mg/kg. The assumption about the neurotoxicity of dapagliflozin at a dose of 50 mg/kg is confirmed by the death of animals after the third administration of the medicine *per se* and especially in combination with sodium valproate.

Empagliflozin (20 mg/kg) and its combination with sodium valproate 150 mg/kg did not show neurotoxicity and therefore are promising for further studies on improving the pharmacotherapy of epilepsy.

The results of studying the anticonvulsant properties of dapagliflozin and its combination with sodium valproate demonstrate the absence of statistically significant anti-epileptic potential *per se*. However, the combination showed better results: the latency prolonged, and the lethality and severity of seizures decreased, but compared to sodium valproate *per se*, this combination is also not perfect, especially considering the revealed neurotoxicity of the medicine.

Our results do not support the data [25] that dapagliflozin reduces the proconvulsant effect of PTZ in rats. This can be explained by the fact that changes in the electroencephalogram were chosen as the main criterion for the effectiveness of dapagliflozin in the cited study. In addition, the dose of PTZ in that experiment was much lower (35 mg/kg) [25], which usually does not cause severe seizures and does not make it possible to fully detect and comprehensively evaluate the anticonvulsant properties of the studied medicines. In a series of experiments with a higher dose of PTZ (70 mg/kg), which causes more pronounced seizures, the authors of the cited study analyzed a small number of indicators of the course of seizures. In particular, as in our experiments, the duration of convulsions decreased; the time to the first myoclonic jerk increased, which also corresponds to an increase in the latency, but these indicators are hardly sufficient for a comprehensive conclusion of the medicine's pro-anticonvulsant properties.

Experiments with empagliflozin indicate the presence of pronounced anticonvulsant properties, which are demonstrated by a significant decrease in lethality by 43 % ($p<0.01$), prolonged latency by 5.9 times ($p<0.05$), a decrease in the number of clonic and tonic attacks compared to control. Even in comparison with the reference anticonvulsant sodium valproate, empagliflozin was not inferior in terms of individual seizure parameters and the main integral indicator of protective action – lethality.

Pronounced anticonvulsant properties were found in sodium valproate (150 mg/kg) in combination with empagliflozin (20 mg/kg). The main integral indicator – animals' lethality reduction – is key for the preclinical stage of developing new methods of treating epilepsy. This indicator decreased to 17 %, which was the best result of all groups and significantly exceeded the effect of sodium valproate ($p<0.05$). In addition, the severity of seizures and the number of seizures in 1 mouse decreased. Considering the absence of neurotoxicity, empagliflozin and its combination with valproate may be useful for the development of new methods of pharmacotherapy for epilepsy.

The mechanisms of the anticonvulsant effect of SGLT-2 inhibitors need to be studied in detail. This direction of experimental epileptology is at the initial stage of development. Therefore there are currently no relevant data. Inhibition of SGLT-2 is not inherent in the mechanism of action of known AEDs. Nevertheless, it can be assumed that SGLT-2 plays a significant role in the deve-

lopment of seizures, and inhibition of this membrane symporter may ensure the survival of neurons in the early stages of epileptogenic processes [24]. The role of the influence of SGLT-2 inhibitors on changes in the provision of neurons with glucose cannot be excluded. It is known that improvement in glycemic control in patients with diabetes and epilepsy is associated with improvement in seizure syndrome [35]. In an experiment in mice, reducing glucose utilization through long-term caloric restriction helps reduce seizure activity [36]. However, the line between anti- and proconvulsant activity in terms of glucose availability for neurons is very thin: a decrease in glucose supply to neurons can provoke convulsions, which is well known in the clinic of hypoglycemic conditions [37].

Thus, the results of this study can form the basis for further elucidation of the mechanisms of the anticonvulsant effect of SGLT-2 inhibitors and for improving the pharmacotherapy of epilepsy, especially when combined with type 2 diabetes or arterial hypertension. Furthermore, in our experiments, it was established for the first time that empagliflozin, an anticonvulsant, has an advantage over dapagliflozin.

Study limitation: This study did not determine the effect of SGLT-2 inhibitors on seizures with different pathogenesis, and the dose dependence of their effect did not measure blood and brain glucose levels.

Further research prospects: Determining the spectrum of anticonvulsant activity, dose dependence and neurochemical mechanisms of action of SGLT-2 inhibitors, interactions with other classic anticonvulsants; study of the effectiveness of SGLT-2 inhibitors in combined models of diabetes and seizure syndrome.

6. Conclusion

1. It was experimentally established that empagliflozin (20 mg/kg) and its combination with sodium valproate (150 mg/kg) does not harm muscle tone and coordination of movements of animals in the rotarod test. In contrast to empagliflozin, dapagliflozin (50 mg/kg), when administered alone and especially when combined with sodium valproate, has a neurotoxic effect.

2. It has been proven that both empagliflozin alone and its combination with sodium valproate exhibit anticonvulsant properties in the model of pentylenetetrazole-induced seizures. However, dapagliflozin, both *per se* and in combination with sodium valproate, does not show pronounced anticonvulsant properties, only slightly, insignificantly reducing individual indicators of seizures and animal lethality.

3. Empagliflozin, in contrast to dapagliflozin, should be recommended for further in-depth studies as a potential anti-epileptic medicine.

Conflict of interest

The authors declare that they have no conflict of interest concerning this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

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Vadim Tsyvunin, PhD, Assistant, Department of Pharmacology and Pharmacotherapy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Sergiy Shtrygol'*, Doctor of Medical Sciences, Professor, Department of Pharmacology and Pharmacotherapy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Ihnat Havrylov, Postgraduate Student, Department of Pharmacology and Pharmacotherapy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Diana Shtrygol', PhD, Associate Professor, Department of Neurology, Psychiatry, Narcology and Medical Psychology, School of Medicine, V. N. Karazin Kharkiv National University, Svobody sq., 4, Kharkiv, Ukraine, 61022

Artur Reus, Network of Pharmacies ANC Lviv, Nezalezhnosti str., 36, Ivano-Frankivsk, Ukraine, 76018

***Corresponding author:** Sergiy Shtrygol', e-mail: shtrygol@ukr.net*