
EXPERIMENTAL
ARTICLES

A Study of the Effect of Derivative of Oximes Pyridine (GIZh-298) on the Contents of Monoamines and Their Metabolites in the Rat Brain during Seizures Induced by Maximal Electroshock

S. A. Litvinova^{a, 1}, B. V. Narkevich^a, I. O. Gaidukov^a, V. S. Kudrin^a, and T. A. Voronina^a

^a*Zakusov Research Institute of Pharmacology, Moscow, Russia*

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Abstract—We studied the effects of the potential antiepileptic agent GIZh-298 and a comparison drug, topiramate, on the concentration of monoamines and their metabolites in the frontal cortex, hypothalamus, nucleus accumbens, striatum, and hippocampus in the rat brain after generalized tonic–clonic seizure caused by electroshock (MES). We found that GIZh-298 (60 mg/kg, i.p.) exhibits a pronounced anticonvulsant effect in the test of MES antagonism and prevents the increase in functional activity of the dopaminergic system and the reduction of the norepinephrine (NE) content in the same structure. Topiramate (100 mg/kg, i.p.), as well as the GIZh-298, prevented the emergence of MES-induced seizures and stimulated an increase in the NA level in the striatum to the normal values but did not affect the MES-induced changes in the functional activity of the dopaminergic system of the nigrostriatal system. Therefore, it may be concluded that the modulation of the noradrenergic neurotransmission in the striatum is one of the mechanisms of the anticonvulsant effect of both GIZh-298 and topiramate in the test of MES antagonism and, in addition, GIZh-298, unlike topiramate, contributes to the reduction of the functional activity of the dopaminergic system in this structure in response to MES.

Keywords: GIZh-298, topiramate, monoamines, dopamine, norepinephrine, brain structures, liquid chromatography, epilepsy, maximal electroshock, MES

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INTRODUCTION

Epilepsy and convulsive disorders are one of the most common neurological diseases of the central nervous system (CNS) whose progression leads to the reduction of the quality of life and disability of the patients. Therefore, the investigation of the mechanisms that underlie the genesis of seizures, as well as the study of the most rational and effective methods of prophylaxis and treatment are one of the major challenges of modern pharmacology.

The accumulating evidence indicates that different brain neurotransmitter systems contribute to the development of convulsive states. The involvement of certain systems depends on the localization of the epileptogenic focus and genetically determined neurochemical connections of this structure with other brain areas [1]. Currently, the systems of aminocidergic neurotransmission play a leading role in the pathogenesis of convulsive disorders: the excitatory system, which includes neurotransmitters such as glutamate and aspartate, and the inhibitory system, which uses

gamma-aminobutyric acid (GABA) and glycine [2–4]. However, the development of seizures involves a significant change in the functioning of other neurotransmitter systems, including the monoaminergic system [5]. Alteration in the dopamine (DA) level is one of the key factors that contribute to the formation and development of various neurological disorders, including epilepsy and epileptiform seizures [6–8]. An increased DA level and changes in the proportion of different subtypes of dopaminergic receptors were observed in all epileptiform states [9, 10].

In previous studies, it has been indicated that the substance GIZh-298 (a derivative of O-(2-R-oxime 4-benzoyl) pyridines) synthesized in the Zakusov Research Institute of Pharmacology has a pronounced antiepileptic effect in the models of chronic focal epilepsy and neurotoxin homocysteine thiolactone-induced seizures and epileptic status in rats with cobalt-induced epileptogenic focus [11, 12]. It has been found that GIZh-298 affects monoaminergic systems of the intact rat brain, which is reflected in a significant decrease in the activity of dopaminergic system in the striatum [13]. The goal of the present study was to investigate the role of the monoaminergic systems of the rat brain in the mechanism of anticon-

¹ Corresponding author; address: ul. Baltiiskaya 8, Moscow, 125315 Russia; phone: +7 (495) 601-21-14, e-mail: sa_litvinova@mail.ru.

vulsive action of GIZh-298 compared to topiramate in rats after a generalized tonic-clonic seizure caused by maximal electroshock (MES).

MATERIALS AND METHODS

The experiments were performed with 60 outbred male rats that weighed 220–230 g (Stolbovaya nursery). The animals were housed in the laboratory vivarium under a 12/12 h light/dark cycle with free access to water and standard pellet feed. To eliminate the effect of circadian rhythm on the neurotransmitter synthesis rate and metabolism, the experiments were performed between the 10 a.m. and 12 p.m.

The MES test is a standard technique that is used for the investigation of primary generalized epilepsy. The main indicators of the potential anticonvulsive activity of the substances in this test is their ability to prevent tonic extension. The comparison drug topiramate (Topamax, pills) and GIZh-298 were administered to the animals intraperitoneally (i.p.) one time at the doses of 100 and 60 mg/kg, respectively, 35 min prior to decapitation. A 0.9% isotonic solution of sodium chloride was injected to the control animals; 30 minutes later, three groups of animals were exposed to electroconvulsive shock through the corneal electrodes and 5 min after MES were decapitated.

The animals were divided into the following groups (the number of animals is indicated in parentheses):

- (1) intact control + physiological solution ($n = 8$),
- (2) GIZh-298 ($n = 8$),
- (3) topiramate ($n = 8$),
- (4) control MES + physiological solution ($n = 8$),
- (5) MES + GIZh-298 ($n = 11$),
- (6) MES + topiramate ($n = 8$).

The MES was applied using a Rodent Shocker RS 221 (Harvard Apparatus, GmbH) device. Electrical stimulation in the form of current discharge (50 Hz, 500 V, 118–120 mA, duration 0.2 s) was administered using corneal electrodes located on the ocular globes of the rats. This resulted in primary generalized seizures with the emergence of clonic convulsions, tonic extension of the fore and hind limbs, and the death of some animals. The scoring system was used to process the data obtained in the maximal electroshock (MES) test, where 0 points is the absence of seizures, 1 point is clonic seizures of the fore and hind limbs, 2 points is tone of the fore limbs and clonic twitching of the hind limbs, 3 points is tonic extensions of the fore and hind limbs.

The animals were decapitated 5 minutes after MES. The brain structures (frontal cortex (FC), hypothalamus, nucleus accumbens (NA), striatum, and hippocampus) were then removed on ice, frozen in liquid nitrogen, and weighed.

Before the experiments on the determination of the neurotransmitter levels, the samples were homoge-

nized using Potter homogenizer (glass-Teflon) in 1 mL of 0.1 N HClO₄ with the addition of 3,4-dioxybenzylamine (0.5 nmol/mL) as an internal standard. The samples then were centrifuged at 10000 g for 10 min. The contents of monoamines and their metabolites norepinephrine (NE), dopamine (DA), 3,4-dioxyphenylacetic acid (DOPAA), homovanillic acid (HVA), serotonin (5-oxytryptamine, 5-OT), and 5-oxyindolylacetic acid (5-OIAA) were determined using the high-performance liquid chromatography technique with electrochemical detection (HPLC/ED) on a LC 304T (BAS, West Lafayette, United States) chromatography with an analytical ReproSil-Pur ODS (C18, 100 mm × 4 mm, 3 μm) (Dr. Maisch, Germany) column at the mobile phase elution velocity of 1.0 mL/min and pressure up to 200 atm. The mobile phase consisted of 0.1 M citrate-phosphate buffer with 1.1 mM octanesulfonic acid, 0.1 mM EDTA, and 9% acetonitrile (pH 3.0). The measurements were performed using an electrochemical detector LC-4B (BA, United States) on a double glass carbon electrode (+0.85 V) against Ag/AgCl reference electrode. The samples were recorded using a Multichrome 1.5 (Ampersend) computer-software complex. All the reagents used for the analysis were of high purity: extra-pure grade or analytical grade.

The processing of the data on the catecholamine content in the brain structures was performed as follows: the normality of data distribution was assessed using the Shapiro–Wilk criterion; since the distribution of the sample means approached a normal distribution, the statistical significance of the differences was evaluated using the two-way analysis of variance followed by Fisher's least significant difference test for multiple comparison. The results we obtained were presented as the mean and standard deviations. The data on the antiepileptic effects of the drugs were processed using the non-parametric Kruskal–Wallis test followed by Dunn's multiple comparison test. The results are presented as mean and standard errors. The data presented in an alternative scale were processed using Fisher's exact test with correction for multiple comparisons. In all the cases, the two-sided criterion with a level of significance of $\alpha = 0.05$ was used.

RESULTS

In 88% of the control animals that were administered physiological solution, the exposure to electroconvulsive shock (MES) caused tonic extension of the fore and hind limbs (group 1, Table 1). GIZh-298 administered at a dose of 60 mg/kg significantly reduced the intensity of MES-induced seizures and the number of animals with complete tonic extension decreased to 28%; correspondingly, there was a significant decrease in the intensity of the seizures according to the score (group 2, Table 1). The comparison drug topiramate administered at a dose of 100 mg/kg, as well as GIZh-298, prevented the emergence of

Table 1. The effect of GIZh-298 (60 mg/kg) and topiramate (100 mg/kg) on the severity of seizures in rats in the MES antagonism test

Animal groups, n	Dose, mg/kg	Intensity of seizures, score	The number of rats with the tone of the fore and hind limbs, %
MES (control), <i>n</i> = 8	—	2.88 ± 0.11	7/8 (87.5)
MES + GIZh-298, <i>n</i> = 11	60	2.18 ± 0.15*	3/11 (28) [#]
MES + topiramate, <i>n</i> = 8	100	2.00 ± 0.18*	1/8 (12.5) [#]

*1 point, clonus of the fore limbs/clonus of the hind limbs; 2 points, tonus of the fore limbs/clonus of the hind limbs; 3 points, tonus of the fore limbs/tonus of the hind limbs; *significant differences compared to the control group (MES), $p \leq 0.05$; [#], significant differences compared to the control group (MES), $p \leq 0.05$ (Fisher's exact test).

MES-induces seizures, which was reflected in a reduction of the number of rats with complete limb tone to 12.5% compared to the number of control animals exposed to MES (Table 1).

In the study of the neurochemical effects of GIZh-298, it was found that the levels of the DA metabolites DOPAA and HVA in the FC increased in intact animals. In the striatum, the index of the dopamine metabolism rate DOPAA/DA decreased, which indicates a reduction of the DA utilization rate in this structure. In addition, changes in the indices of serotonergic neurotransmission were observed: the level of the serotonin metabolite 5-OIAA in the hippocampus and hypothalamus, as well as the value of the 5-OIAA/5-OT index in the striatum, increased, which reflects the intensification of serotonin utilization in this structure (Table 2).

Topiramate did not affect catecholamine levels in the FC, striatum, and hippocampus, but changed the concentrations of DA metabolites, although the level of DA remained constant. An increase in the DOPAA level and in HVA/DA index was observed in the NA and hypothalamus, respectively.

Exposure to MES caused significant alterations in the neurochemical parameters of the noradrenergic, dopaminergic, and serotonergic systems. In the FC, hypothalamus, NA, and striatum, an increase in the content of the DA metabolites DOPAA (in the FC, NA, and striatum) and HVA (in the NA and striatum), as well as in the indices of their metabolism, DOPAA/DA (in the hypothalamus, NA, and striatum) and HVA/DA (in the NA and striatum) was observed; this reflects an increased functional activity of the dopaminergic system in the brain structures that are related to different neuronal pathways. MES led to a decrease in the NA levels in the FC by 10% and by 27.5% in the striatum. The change in the activity of the serotonergic system was observed in the hippocampus and striatum: both the 5-OIAA level and the 5-OIAA/5-OT index, which reflects the rate of serotonin utilization, increased (Table 2).

The administration of GIZh-298 prior to MES affected the indices of both dopaminergic and noradrenergic systems. A decrease in the DOPAA/DA and HVA/DA indices in the striatum was observed,

whereas in the group of rats exposed to MES these indices increased. Analogously, GIZh-298 prevented MES-induced reduction of the NA level in the striatum by increasing the neurotransmitter content to the values of intact control. The effect of GIZh-298 on the activity of the serotonergic system in MES-exposed rats was less pronounced. The level of 5-OIAA increased in the hippocampus, whereas in animals treated with GIZh-298 without exposure to MES, this index increased together with the 5-OIAA/5-OT value (Table 2).

Similar to GIZh-298, topiramate administered at a dose of 100 mg/kg caused an increase in the NA level in the striatum. However, unlike GIZh-298, it did not affect the DOPAA/DA and HVA/DA indices of dopamine metabolism in this structure, which increased in the group of animals with seizures (the control group exposed to MES). In addition, an increase in the 5-OIAA level in the hippocampus was observed in response to administration of both topiramate and GIZh-298 (Table 2).

DISCUSSION

The results of the experiments demonstrated that GIZh-298 (60 mg/kg/ i.p.) exhibits a pronounced anticonvulsive effect in the test of MES antagonism. The study of the changes in the neurotransmitters in the brain structures of rats exposed to MES found that GIZh-298 prevents the increase in the functional activity of the dopaminergic system in the striatum and the decrease in the norepinephrine (NE) content in the same structure. Topiramate administered at a dose of 100 mg/kg, as well as GIZh-298, impedes the development of MES-induced convulsive attack and increases the NA level above the normal values, although it does not correct the changes in the functional activity of the dopaminergic nigrostriatal and/or mesolimbic systems. The role of NA in seizure modulation and in the mechanism of action of other antiepileptic agents (AEA) is known since 1980. The anticonvulsive effect of AEA's such as phenytoin, carbamazepine, phenobarbital, and valproate disappears in animals after the destruction of noradrenergic (NE) neurons. In contrast, an increase in the antiepileptic activity of the aforementioned drugs was observed in

Table 2. The effects of GIZh-298 and topiramate on the level of monoamines and their metabolites in the brain structures of inbred rats in the model of maximal electroshock (MES)

Animal groups	DA	DOPAA	HVA	3-MT	DOPAA/DS	HVA/DA	NE	5-OT	5-OIAA	5-OIAA/ 5-OT
Frontal cortex										
Control	0.38 ± 0.05	0.15 ± 0.01	0.16 ± 0.01	BDL	0.44 ± 0.06	0.49 ± 0.07	1.35 ± 0.04	4.30 ± 0.16	2.81 ± 0.18	0.65 ± 0.03
MES	0.30 ± 0.02	0.18 ± 0.01*	0.18 ± 0.02	BDL	0.60 ± 0.03*	0.58 ± 0.06	1.21 ± 0.04*	4.45 ± 0.21	3.29 ± 0.14*	0.74 ± 0.04
GIZh-298	0.34 ± 0.03	0.18 ± 0.01*	0.25 ± 0.02*	BDL	0.55 ± 0.03	0.76 ± 0.12	1.36 ± 0.06	4.26 ± 0.19	3.09 ± 0.14	0.73 ± 0.04
MES + GIZh-298	0.39 ± 0.04	0.19 ± 0.00**	0.23 ± 0.03*	BDL	0.53 ± 0.04	0.62 ± 0.07	1.25 ± 0.04	4.52 ± 0.08	3.53 ± 0.08**	0.78 ± 0.02**
TM	0.36 ± 0.03	0.16 ± 0.01	0.16 ± 0.02	BDL	0.46 ± 0.04	0.45 ± 0.05	1.32 ± 0.06	4.31 ± 0.17	3.10 ± 0.10	0.73 ± 0.05
MES + TM	0.43 ± 0.04#	0.19 ± 0.01**	0.22 ± 0.02	BDL	0.46 ± 0.05#	0.56 ± 0.07	1.26 ± 0.04	4.47 ± 0.10	3.57 ± 0.11**	0.80 ± 0.03**
Hypothalamus										
Control	2.50 ± 0.18	0.39 ± 0.03	0.14 ± 0.04	0.12 ± 0.06	0.16 ± 0.01	0.05 ± 0.01	6.48 ± 0.71	5.16 ± 0.49	6.74 ± 0.71	1.30 ± 0.03
MES	1.98 ± 0.18	0.46 ± 0.05	0.23 ± 0.06	0.08 ± 0.02	0.24 ± 0.02**	0.11 ± 0.03*	6.72 ± 0.26	5.41 ± 0.20	7.75 ± 0.31	1.44 ± 0.05
GIZh-298	2.16 ± 0.12	0.42 ± 0.02	0.26 ± 0.03	0.11 ± 0.03	0.20 ± 0.01	0.12 ± 0.02*	6.80 ± 0.34	5.58 ± 0.16	8.12 ± 0.25*	1.46 ± 0.06
MES + GIZh-298	2.26 ± 0.18	0.47 ± 0.03	0.35 ± 0.05**	0.13 ± 0.02	0.22 ± 0.02*	0.16 ± 0.02**	6.26 ± 0.23	5.50 ± 0.15	7.75 ± 0.22*	1.41 ± 0.04
TM	2.93 ± 0.36	0.51 ± 0.06*	0.23 ± 0.02	0.09 ± 0.02	0.19 ± 0.00	0.08 ± 0.01	7.19 ± 0.60	5.76 ± 0.17	7.94 ± 0.26*	2.16 ± 0.74
MES + TM	2.81 ± 0.38	0.52 ± 0.03*	0.30 ± 0.08*	0.09 ± 0.02	0.20 ± 0.02	0.10 ± 0.02	6.63 ± 0.45	6.07 ± 0.36*	8.87 ± 0.34**#	1.48 ± 0.07
Nucleus accumbens										
Control	13.20 ± 0.73	1.51 ± 0.09	0.67 ± 0.07	0.08 ± 0.02	0.11 ± 0.00	0.05 ± 0.00	0.81 ± 0.09	1.39 ± 0.09	0.88 ± 0.06	0.65 ± 0.05
MES	13.64 ± 0.91	1.85 ± 0.16*	0.91 ± 0.10*	0.10 ± 0.02	0.14 ± 0.01**	0.07 ± 0.00**	0.80 ± 0.12	1.47 ± 0.13	0.97 ± 0.08	0.67 ± 0.04
GIZh-298	13.51 ± 0.86	1.55 ± 0.11	0.75 ± 0.04	0.07 ± 0.02	0.11 ± 0.00	0.06 ± 0.00	0.81 ± 0.10	1.45 ± 0.13	0.92 ± 0.06	0.65 ± 0.04
MES + GIZh-298	13.25 ± 1.09	1.69 ± 0.13	0.86 ± 0.06*	0.15 ± 0.07	0.13 ± 0.00*	0.07 ± 0.00**	0.92 ± 0.14	1.43 ± 0.09	0.95 ± 0.05	0.67 ± 0.02
TM	13.12 ± 0.63	1.65 ± 0.09	0.86 ± 0.05	0.04 ± 0.01	0.12 ± 0.00	0.065 ± 0.00*	0.91 ± 0.13	1.42 ± 0.14	0.96 ± 0.07	0.69 ± 0.04
MES + TM	12.10 ± 0.66	1.76 ± 0.06	0.85 ± 0.04	0.07 ± 0.03	0.15 ± 0.01**	0.07 ± 0.01**	1.15 ± 0.21	1.40 ± 0.14	1.00 ± 0.06	0.74 ± 0.04
Striatum										
Control	61.16 ± 3.37	5.70 ± 0.29	61.16 ± 3.37	1.09 ± 0.09	0.09 ± 0.00	0.06 ± 0.00	0.72 ± 0.04	2.92 ± 0.17	3.08 ± 0.13	1.07 ± 0.04
MES	59.19 ± 1.81	6.73 ± 0.27*	59.19 ± 1.81*	0.88 ± 0.11	0.11 ± 0.00**	0.08 ± 0.00**	0.52 ± 0.04*	2.60 ± 0.13	3.39 ± 0.12	1.32 ± 0.07*
GIZh-298	63.34 ± 3.86	5.31 ± 0.43	63.34 ± 3.86	0.66 ± 0.10	0.08 ± 0.00*	0.07 ± 0.00	0.70 ± 0.10	2.81 ± 0.19	3.29 ± 0.20	1.18 ± 0.04
MES + GIZh-298	60.69 ± 2.85	6.60 ± 0.36*	60.69 ± 2.85	0.80 ± 0.09	0.10 ± 0.00#	0.07 ± 0.00#	0.71 ± 0.06#	2.92 ± 0.11	3.46 ± 0.14	1.19 ± 0.04
TM	54.55 ± 2.35	5.10 ± 0.25	54.55 ± 2.35	1.00 ± 0.20	0.09 ± 0.00	0.06 ± 0.01	0.75 ± 0.08	2.32 ± 0.37	2.98 ± 0.28	1.15 ± 0.04
MES + TM	55.17 ± 3.35	6.68 ± 0.32*	55.17 ± 3.35	1.09 ± 0.13	0.12 ± 0.01*	0.09 ± 0.00	1.00 ± 0.07**	3.22 ± 0.26	3.58 ± 0.28	1.12 ± 0.07##
Hippocampus										
Control	0.18 ± 0.03	0.11 ± 0.01	0.08 ± 0.01	BDL	3.12 ± 0.10	0.60 ± 0.16	1.84 ± 0.06	3.12 ± 0.10	4.14 ± 0.17	1.33 ± 0.04
MES	0.19 ± 0.03	0.13 ± 0.01	0.06 ± 0.01	BDL	3.21 ± 0.28	0.38 ± 0.11	1.58 ± 0.06	3.21 ± 0.28	4.13 ± 0.13	1.41 ± 0.05
GIZh-298	0.15 ± 0.02	0.13 ± 0.01	0.07 ± 0.01	BDL	3.33 ± 0.29	0.65 ± 0.24	1.74 ± 0.13	3.33 ± 0.29	5.04 ± 0.37**	1.53 ± 0.08*
MES + GIZh-298	0.18 ± 0.02	0.13 ± 0.01	0.07 ± 0.02	BDL	3.31 ± 0.07	0.45 ± 0.12	1.76 ± 0.07	3.31 ± 0.07	4.91 ± 0.15#	1.49 ± 0.04
TM	0.22 ± 0.08	0.16 ± 0.02*	0.05 ± 0.02	BDL	3.31 ± 0.31	0.33 ± 0.14	1.93 ± 0.17	3.31 ± 0.31	4.56 ± 0.26	1.41 ± 0.08
MES + TM	0.20 ± 0.02	0.15 ± 0.01*	0.06 ± 0.02	BDL	3.50 ± 0.30	0.36 ± 0.13	1.85 ± 0.19	3.50 ± 0.30	5.04 ± 0.24**#	1.47 ± 0.07

The mean values and standard errors are presented ($M \pm S.E.M.$). BDL, below the detection limit; TM, topiramate. **Significant differences compared to the intact control without MES, $p \leq 0.01$; * $p \leq 0.05$ (two-way ANOVA); ## significant differences compared to the control with MES, $p \leq 0.01$; # $p \leq 0.05$ (two-way ANOVA).

combination with the agents which enhance the activity of the central noradrenergic neurotransmission [14–16]. These data demonstrate a significant role of NE in realization of antiepileptic activity and AEA action. We found that the exposure to MES leads to a statistically significant decrease in NE level in two structures, in the FC (by 10%) and more substantially in the striatum (by 28%) which may reflect the biological role of NE in a given structure during the emergence of seizures.

It is known that electric shock therapy is one of the most effective methods of treatment of drug-resistant depression and it is used in therapy of depressive disorders due to the ability of electric shock to significantly increase DA release. It had been previously found that convulsive electric shock mainly affects striatal dopaminergic system. In the first minute after electric shock stimulation, the levels of DA and its metabolites in the striatum of animals increased [17–20]. The data obtained in the present study confirm the increase in the functional activity of the dopaminergic system which is reflected in the intensification of DA metabolism rate in the FC, hypothalamus, NA, and striatum 5 min after exposure to MES.

An increase in the DA level in the nigrostriatal level was demonstrated in different experimental models of epilepsy [9, 10, 21]. As an example, in the Krushinskii–Molodkina (KM) rat strain with genetically determined susceptibility to audiogenic seizure, there is an elevated DA level and reduced number of D2-receptors in the striatum, and sound-induced seizures are accompanied by an increase in the activity of the dopaminergic nigrostriatal system [5, 6, 22]. The same changes were observed in the pilocarpine epilepsy model [21, 23, 24]. Since DA is known to inhibit the neuronal excitability by affecting D2-receptors which are functionally belong to so-called antiepileptic system, some authors propose an increase in the functional activity of the dopaminergic system in seizure initiation to be a compensatory reaction which suppresses convulsive states [25–28]. This is confirmed by the fact that the DA level decreases during interictal period in rats with epileptiform activity which was proposed to be associated with its depleting increase during the seizures [29–31]. Recently, striatum has been viewed as a key element in GABAergic regulation of convulsive activity [28, 32, 33]. In addition, the pattern of response of GABAergic striatal neurons to the stimulating effect of glutamatergic neurons is determined by the balance of dopamine receptors and is in close interaction with dopaminergic system of the substantia nigra (SN). Most of the neurons in this structure send their axons to the striatum, thus comprising a nigrostriatal pathway which plays a role in regulation of a wide spectrum of behavioral responses, including the formation of epileptiform activity [28, 32, 34, 35].

Analysis of the effects of these drugs suggests that one of the components in the mechanism of anticonvulsive action of GIZh-298 and topiramate in the test of MES antagonism is the modulation of noradrenergic neurotransmission in the striatum. In addition, GIZh-298, unlike topiramate, also contributes to the attenuation of the functional activity of the dopaminergic system in this structure increased in response to exposure to MES.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare that they have no conflict of interest.

Ethical approval. The study was organized and implemented in accordance with Order of the Ministry of Health of Russia no. 199 of April 1, 2016 On Approval of the Rules for Good Laboratory Practice. The animals were kept in accordance with Sanitary Regulations 2.2.1.3218-14 Sanitary and epidemiological requirements for organization, equipment, and maintenance of experimental biological clinics (vivaria) of August 29, 2014, no. 51. The experiments were approved by the Biomedical Ethics Commission of the Zakusov Institute of Pharmacology (Protocol no. 6 of April 16, 2018).

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