Research Results in Pharmacology

Research Results in Pharmacology 7(3): 15–22
UDC: 611.08:615.21:599.3/.8
DOI 10.3897/rrpharmacology.7.68001

Research Article

Antiamnestic effect of new nicotinic acid derivatives

Victor V. Yasnetsov[1,3], Diana E. Kaurova[2], Sofia Ya. Skachilova[1], Evgeniy Yu. Bersenev[3]

1 *All-Union Research Center for Safety of Biologically Active Substances, 23 Kirova St., Staraya Kupavna, Moscow Region 142450, Russia*
2 *State University of Humanities and Technology, 22 Zelenaya St., Orekhovo-Zuevo, Moscow Region 142611, Russia*
3 *State Scientific Center of Russian Federation – Institute of Biomedical Problems of the Russian Academy of Sciences, 76A Khoroshevskoe Rd., Moscow 123007, Russia*

Corresponding author: Victor V. Yasnetsov (vicyas@yandex.ru)

Academic editor: Oleg Gudyrev ♦ **Received** 28 April 2021 ♦ **Accepted** 15 June 2021 ♦ **Published** 7 September 2021

Citation: Yasnetsov VV, Kaurova DE, Skachilova SYa, Bersenev EYu (2021) Antiamnestic effect of new nicotinic acid derivatives. Research Results in Pharmacology 7(3): 15–22. https://doi.org/10.3897/rrpharmacology.7.68001

Abstract

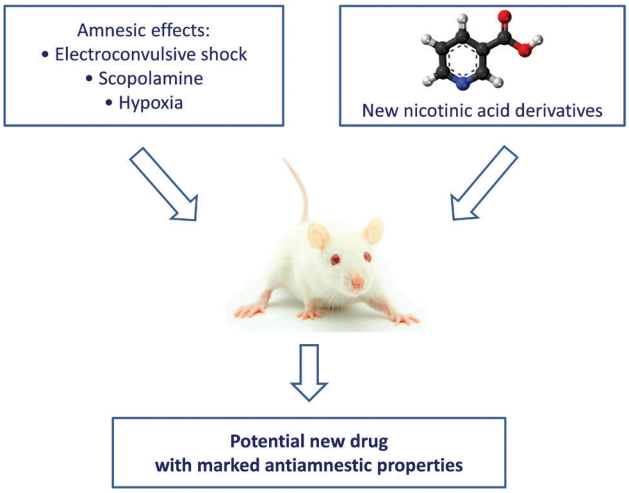
Introduction: The search for new drugs for the prevention and treatment of vascular cognitive disorders continues to be a relevant task of pharmacology. In this regard, the aim of this work is to study the antiamnestic effect of five new nicotinic acid derivatives in comparison with the well-known drug mexidol (ethylmethylhydroxypyridine succinate) in animals.

Materials and methods: The experiments were carried out on white male mice using conditioned passive avoidance reflex (CPAR). Electroconvulsive shock (ECS), scopolamine administration, and acute hypoxia in a hermetic chamber were used as amnesic effects. Testing for the safety of CPAR was performed 24 h after amnesic exposure. The new substances, reference drug mexidol, and a 0.9% sodium chloride solution (control group) were administered once intraperitoneally 60 min before mice training.

Results and discussion: Three of the five new nicotinic acid derivatives, LKhT 4-19 (100 mg/kg), LKhT 6-19 (25, 50, and 100 mg/kg), and LKhT 7-19 (100 mg/kg), have antiamnestic properties on models of amnesia in mice induced by ESC, scopolamine, and acute hypoxia in a hermetic chamber. At the same time, the most efficient substance – LKhT 6-19 – exceeds the reference drug mexidol on all three models used. In addition, this compound is also more efficient than two other new compounds, LKhT 4-19 and LKhT 7-19, on the model of ESC-induced amnesia and LKhT 7-19 on the scopolamine-induced amnesia model.

Conclusion: Compound LKhT 6-19 is promising for further advanced preclinical studies as a potential drug with antiamnestic activity.

Graphical abstract:



Keywords

amnesia, conditioned passive avoidance reflex, mice, new nicotinic acid derivatives.

Introduction

The number of patients with ischemic cerebrovascular diseases at present continues to increase in most countries in the world (Skvortsova et al. 2018, Stakhovskaya and Kotov 2018, Mendelson and Prabhakaran 2021). On the one hand, this is due to an increase in life expectancy and the number of elderly people and, on the other hand, to the fact that cerebrovascular disorders occur in employable and socially active middle-aged people more and more frequently, being among the leading causes of partial or complete disability (Tabeeva 2019a, Putaala 2020).

A significant contribution to the disablement of patients with this pathology is made by cognitive disorders that are diverse in severity and clinical manifestations (Belskaya et al. 2016, Parfenov 2019, Kotov et al. 2020, Frantellizzi et al. 2021), ranging from mild forms to dementia. In addition, patients with moderate post-stroke cognitive impairment may suffer a wide range of disorders, including memory loss (Kulesh and Shestakov 2016). This leads to the deterioration in life quality, a violation of a person's domestic, social and professional activity, and sometimes to complete dependence on others (Bogolepova and Levin 2020).

It should also be noted that cognitive impairment develops as a result of ischemic brain damage in the severe course of the new coronavirus infection COVID-19 (Miners et al. 2020).

Despite the improvement of pharmacotherapy of vascular cognitive impairments, the majority of the drugs used today are either insufficiently efficient or cause a number of side effects that limit their long-term and widespread use (Sun 2018, Van der Flier et al. 2018, Tabeeva 2019b). Therefore, the search for new drugs for the prevention and treatment of vascular cognitive disorders continues to be relevant.

Therefore, our focus was on new nicotinic acid derivatives. As is known, nicotinic acid has been widely used since the middle of the XX century as a drug that has anti-inflammatory, hypolipidemic, anti-atherogenic, neuroprotective, and vasodilating effects, including those on brain vessels, as well as other valuable pharmacological properties (Gasperi et al. 2019, Sharma and Madan 2019). However, presently nicotinic acid is not used for pharmacotherapy of cerebrovascular diseases and their consequences due to severe side effects.

We have previously shown that one of the five new nicotinic acid derivatives, LKhT 6-19, was the most efficient on a model of acute hypoxia in a hermetic chamber in mice. This derivative provided an action depending on the dose, surpassing the severity of the effect of the well-known domestic drug mexidol (Yasnetsov et al. 2020).

Therefore, the aim of this work was to study the antiamnestic effect of five new nicotinic acid derivatives in comparison with mexidol in animals.

Materials and methods

Animals

The experiments were carried out on 1033 white male BALB/c mice weighing 20–24 g (Andreevka Nursery, Branch of the Scientific Center of Biomedical Technologies of the Federal Medical-Biological Agency of Russia, Moscow Region, Russia). The care for animals and conducting experiments were in compliance with Order No. 199n of the Ministry of Health of the Russian Federation of April 1, 2016 "On Approval of the Rules of Good Laboratory Practice". The experiments were approved by the Bioethics Commission of the All-Union Research Center for Safety of Biologically Active Substances (Minutes No. 20/2020 of September 21, 2020).

Substances and reference drug

Five new nicotinic acid derivatives synthesized at the Department of Chemistry and Technology of Synthetic Drugs and Analytical Control of the All-Union Research Center for Safety of Biologically Active Substances (Russia) were studied. The chemical names of the compounds are given in Table 1.

Table 1. New Nicotinic Acid Derivatives

Laboratory code	Chemical name
LKhT 4-19	Bis (-2-aminium ethanesulfonate magnesium)-3-pyridinecarbonoate
LKhT 6-19	Magnesium-bis(-3-pyridinecarbonoate)
LKhT 7-19	3-pyridinecarboxamide-2-aminoethanesulfonic acid
LKhT 9-19	5-bromo-3-pyridinecarboxamide-2-amino-5-ethyl-1,3,4-thiadiazole
LKhT 13-19	3-pyridinecarboxamide-2-amino-5-methylpyridine

All the substances are white microcrystalline powders with a slight odor. The compounds were dissolved in a 0.9% sodium chloride (NaCl) solution. In the case of insufficient solubility of substances, 1–2 droplets of Tween-80 were added to the solutions.

We used mexidol (ethylmethylhydroxypyridine succinate, in the form of substance; "Pharmasoft", Russia) as a reference drug. This is a derivative of 3-hydroxypyridine, which, like the studied substances, contains the pyridine

heterocycle in its structure and is also widely used today in neurology in the treatment of vascular cognitive disorders (Voronina 2016).

Experimental methods

The antiamnestic effect of new nicotinic acid derivatives was studied in mice using the conditioned passive avoidance reflex (CPAR) of electrocutaneous irritation (Voronina et al. 2012).

The CPAR production in mice was carried out on the basis of electrocutaneous reinforcement according to the method by Cumin et al. (1982) taking into account the recommendations by Mondadori et al. (1990). The tests were conducted in an experimental black chamber 30×40×30 cm in size, with an electrode floor and a white plastic platform (7.5×7.5×0.5 cm), which was placed on the floor in the center of the chamber. The mice were placed onto the plastic platform, one at a time. Usually, the animals descended or jumped from the platform onto the electrode floor, where they were subjected to an electric shock as a "punishment" (at that time, direct electric current of 0.5 mA was applied to the floor of the chamber). The electric current was switched on only when the mouse touched the floor with all four limbs. The usual reaction of the animals was to return to the safe platform. After 5 min of training, the mice developed CPAR: they remained on the platform. Testing for the retention of CPAR was performed 24 h after the amnesic exposure. But if the animal left the platform within 1 min, it was registered as having retrograde amnesia of CPAR.

The electroconvulsive shock (ECS; electric current parameters: 50 Hz, 50 mA, 0.3 s), administration of scopolamine (Sigma-Aldrich) at a dose of 1 mg/kg intraperitoneally, and acute hypoxia in a hermetic chamber (13–15-min stay of mice in a hermetic 200-cm^3 chamber) were used as amnesic effects.

New nicotinic acid derivatives, reference drug mexidol, and a 0.9% NaCl solution (control group) were administered once intraperitoneally 60 min before mice training.

The choice of doses of the studied compounds was dictated by the results of previous experiments, in particular, to study their antihypoxic activity (Yasnetsov et al. 2020).

Statistical analysis

Statistic processing of the obtained data was performed using BioStat 2009 Professional software by the nonparametric method, Fisher's exact test. The differences were considered statistically significant at $p < 0.05$.

Results and discussion

The effect of new nicotinic acid derivatives on the model of electroconvulsive shock-induced amnesia in mice

It was found that the majority (87%; $p < 0.001$) of the mice had retrograde amnesia of conditioned passive avoidance reflex 24 h after exposure to ECS (Table 2).

The new nicotinic acid derivative LKhT 4-19 at a dose of 25 mg/kg did not significantly affect amnesia of CPAR, and at doses of 50 and 100 mg/kg significantly weakened the amnesic effect by 1.5 ($p < 0.05$) and 2.7 times ($p < 0.001$), respectively.

Another new substance, LKhT 6-19, was efficient in all three doses tested. Thus, it significantly ($p < 0.001$) reduced the severity of amnesia at a dose of 25 mg/kg by 3.1 times and at doses of 50 and 100 mg/kg completely prevented amnesia development.

Table 2. The Effect of New Nicotinic Acid Derivatives and the Reference Drug Mexidol on Amnesia in Mice Induced by Electroconvulsive Shock (ECS)

Experimental conditions and substance (dose, mg/kg)	Total number of mice	Number of mice trained of conditioned passive avoidance reflex (%)	Number of mice with amnesia in passive avoidance test 24 h after exposure to ECS (%)
0.9% NaCl solution + false ECS (control 1)	25	24 (96)	4 (17)
0.9% NaCl solution + ECS (control 2)	25	24 (96)	21 (87)°°°
LKhT 4-19 (25) + ECS	15	14 (93)	9 (64)°°
LKhT 4-19 (50) + ECS	15	14 (93)	8 (57)*
LKhT 4-19 (100) + ECS	20	19 (95)	6 (32)***
LKhT 6-19 (25) + ECS	19	18 (95)	5 (28)***$^{\#}$
LKhT 6-19 (50) + ECS	27	26 (96)	4 (15)***$^{\#\&\&\S\S}$
LKhT 6-19 (100) + ECS	27	26 (96)	3 (12)***§§
LKhT 7-19 (25) + ECS	12	11 (92)	8 (73)°°
LKhT 7-19 (50) + ECS	12	11 (92)	7 (64)°°
LKhT 7-19 (100) + ECS	15	14 (93)	8 (57)*
LKhT 9-19 (25) + ECS	10	9 (90)	7 (78)°°
LKhT 9-19 (50) + ECS	10	9 (90)	6 (67)°
LKhT 9-19 (100) + ECS	15	14 (93)	9 (64)°°
LKhT 13-19 (25) + ECS	10	9 (90)	6 (67)°
LKhT 13-19 (50) + ECS	10	9 (90)	6 (67)°
LKhT 13-19 (100) + ECS	15	14 (93)	9 (64)°
Mexidol (25) + ECS	21	20 (95)	12 (60)*
Mexidol (50) + ECS	26	25 (96)	10 (40)***
Mexidol (100) + ECS	20	19 (95)	4 (21)***

Note: differences are significant compared to control 1 and control 2 groups of animals, respectively: ° or * – $p < 0.05$, °° or ** – $p < 0.01$, °°° or *** – $p < 0.001$. Differences between LKhT 6-19 and: mexidol in similar doses: $^{\#}$ – $p < 0.05$; LKhT 4-19 at a dose of 50 mg/kg: $^{\&\&}$ – $p < 0.01$; LKhT 7-19 at a dose of 100 mg/kg: §§ – $p < 0.01$ (Fisher's exact test).

The compound LKhT 7-19 at doses of 25 and 50 mg/kg did not significantly affect amnesia of CPAR and at a dose of 100 mg/kg significantly ($p < 0.05$) weakened the amnesic effect by 1.5 times.

Two other new substances, LKhT 9-19 and LKhT 13-19 (25, 50, and 100 mg/kg), were inefficient.

The reference drug mexidol had antiamnestic properties in all three tested doses: at doses of 25 and 50 mg/kg it significantly reduced the severity of amnesia by 1.4 ($p < 0.05$) and 2.2 times ($p < 0.001$), respectively, and at a dose of 100 mg/kg almost completely prevented its development.

In terms of the severity of the antiamnestic effect, LKhT 6-19 at doses of 25 and 50 mg/kg significantly ($p < 0.05$) exceeded mexidol at similar doses by 2.1 and 2.7 times, respectively, and at a dose of 50 mg/kg acted in the same way as mexidol at a dose of 100 mg/kg. In addition, LKhT 6-19 at doses of 50 and 100 mg/kg significantly ($p < 0.01$) exceeded LKhT 7-19 at a dose of 100 mg/kg by 3.8 and 4.8 times, respectively, and at a dose of 50 mg/kg exceeded LKhT 4-19 at a similar dose by 3.8 times.

Therefore, three of the five new nicotinic acid derivatives, LKhT 4-19 (50 and 100 mg/kg), LKhT 6-19 (25, 50, and 100 mg/kg), and LKhT 7-19 (100 mg/kg), have antiamnestic properties on the model of ECS-induced amnesia in mice. At the same time, the most efficient substance LKhT 6-19 is superior in the intensity of the action to both the well-known drug mexidol and two other new compounds, LKhT 4-19 and LKhT 7-19.

The effect of new nicotinic acid derivatives on the model of scopolamine-induced amnesia in mice

It was shown that the majority (79%; $p < 0.001$) of mice had retrograde amnesia of CPAR 24 h after scopolamine administration (Table 3).

The new nicotinic acid derivative LKhT 4-19 at doses of 25 and 50 mg/kg did not significantly affect the severity of amnesia and at a dose of 100 mg/kg significantly ($p < 0.001$) reduced it by 3.0 times.

The compound LKhT 6-19 as in the previous model of amnesia was efficient in all three tested doses: it significantly ($p < 0.001$) weakened the amnesic effect at a dose of 25 mg/kg by 3.0 times and at doses of 50 and 100 mg/kg completely prevented its development.

LKhT 7-19 at doses of 25 and 50 mg/kg did not significantly affect the severity of amnesia and at a dose of 100 mg/kg significantly ($p < 0.05$) reduced it by 1.8 times.

The substances LKhT 9-19 and LKhT 13-19 (25, 50, and 100 mg/kg) were inefficient.

The reference drug mexidol had an antiamnestic effect at doses of 50 and 100 mg/kg, at the first dose significantly reducing the severity of amnesia by 1.9 times ($p < 0.001$) and at the second dose completely preventing its development. At a dose of 25 mg/kg this drug was inefficient.

In terms of the intensity of the antiamnestic effect, LKhT 6-19 at doses of 25 and 50 mg/kg significantly ($p < 0.05$) exceeded mexidol at similar doses by 2.2 and 2.6 times, respectively, and at a dose of 50 mg/kg acted as mexidol at a dose of 100 mg/kg. In addition, LKhT 6-19 at a dose of 100 mg/kg significantly ($p \leq 0.05$) exceeded LKhT 7-19 at a similar dose.

Therefore, three of the five new nicotinic acid derivatives, LKhT 4-19 (100 mg/kg), LKhT 6-19 (25, 50, and 100 mg/kg), and LKhT 7-19 (100 mg/kg), have the antiamnestic properties on the model of scopolamine-induced amnesia in mice. At the same time, the most efficient substance LKhT 6-19 is superior in the intensity of the action to both mexidol and LKhT 7-19.

Table 3. The Effect of New Nicotinic Acid Derivatives and the Reference Drug Mexidol on Scopolamine-induced Amnesia in Mice

Experimental conditions and substance (dose, mg/kg)	Total number of mice	Number of mice trained of conditioned passive avoidance reflex (%)	Number of mice with amnesia in passive avoidance test 24 h after scopolamine administration (%)
0.9% NaCl solution + 0.9% NaCl solution (control 1)	26	25 (96)	4 (16)
0.9% NaCl solution + scopolamine (control 2)	25	24 (96)	19 (79)°°°
LKhT 4-19 (25) + scopolamine	12	11 (92)	6 (55)°
LKhT 4-19 (50) + scopolamine	15	14 (93)	7 (50)°
LKhT 4-19 (100) + scopolamine	20	19 (95)	5 (26)***
LKhT 6-19 (25) + scopolamine	20	19 (95)	5 (26)***#
LKhT 6-19 (50) + scopolamine	26	25 (96)	4 (16)***#
LKhT 6-19 (100) + scopolamine	24	23 (96)	3 (13)***§
LKhT 7-19 (25) + scopolamine	12	11 (92)	7 (64)°°
LKhT 7-19 (50) + scopolamine	15	14 (93)	7 (50)°
LKhT 7-19 (100) + scopolamine	15	14 (93)	6 (43)*
LKhT 9-19 (25) + scopolamine	10	9 (90)	6 (67)°°
LKhT 9-19 (50) + scopolamine	10	9 (90)	5 (56)°
LKhT 9-19 (100) + scopolamine	15	14 (93)	7 (50)°
LKhT 13-19 (25) + scopolamine	10	9 (90)	5 (56)°
LKhT 13-19 (50) + scopolamine	12	11 (92)	6 (55)°
LKhT 13-19 (100) + scopolamine	15	14 (93)	7 (50)°
Mexidol (25) + scopolamine	20	19 (95)	11 (58)°°
Mexidol (50) + scopolamine	25	24 (96)	10 (42)**
Mexidol (100) + scopolamine	20	19 (95)	3 (16)***

Note: differences are significant compared to control 1 and control 2 groups of animals, respectively: ° or * – $p < 0.05$, °° or ** – $p < 0.01$, °°° or *** – $p < 0.001$. Differences between LKhT 6-19 and: mexidol in similar doses: # – $p < 0.05$; LKhT 7-19 at a dose of 100 mg/kg: § – $p \leq 0.05$ (Fisher's exact test).

Table 4. The Effect of New Nicotinic Acid Derivatives and the Reference Drug Mexidol on Amnesia in Mice Induced by Acute Hypoxia in the Hermetic Chamber

Experimental conditions and substance (dose, mg/kg)	Total number of mice	Number of mice trained of conditioned passive avoidance reflex (%)	Number of mice with amnesia in passive avoidance test 24 h after hypoxia (%)
0.9% NaCl solution + false hypoxia (control 1)	25	24 (96)	4 (17)
0.9% NaCl solution + hypoxia (control 2)	25	24 (96)	17 (71)°°°
LKhT 4-19 (25) + hypoxia	15	14 (93)	7 (50)°
LKhT 4-19 (50) + hypoxia	15	14 (93)	6 (43)
LKhT 4-19 (100) + hypoxia	20	19 (95)	5 (26)**
LKhT 6-19 (25) + hypoxia	20	19 (95)	4 (21)**#
LKhT 6-19 (50) + hypoxia	24	23 (96)	4 (17)***
LKhT 6-19 (100) + hypoxia	24	23 (96)	3 (13)***
LKhT 7-19 (25) + hypoxia	12	11 (92)	6 (54)°
LKhT 7-19 (50) + hypoxia	12	11 (92)	5 (45)
LKhT 7-19 (100) + hypoxia	15	14 (93)	5 (36)*
LKhT 9-19 (25) + hypoxia	10	9 (90)	6 (67)°
LKhT 9-19 (50) + hypoxia	10	9 (90)	6 (67)°
LKhT 9-19 (100) + hypoxia	15	14 (93)	8 (57)°
LKhT 13-19 (25) + hypoxia	10	9 (90)	6 (67)°
LKhT 13-19 (50) + hypoxia	10	10 (90)	5 (50)
LKhT 13-19 (100) + hypoxia	15	14 (93)	6 (43)
Mexidol (25) + hypoxia	20	19 (95)	10 (53)°
Mexidol (50) + hypoxia	20	19 (95)	4 (21)**
Mexidol (100) + hypoxia	20	19 (95)	3 (16)***

Note: differences are significant compared to control 1 and control 2 groups of animals, respectively: ° or * – $p < 0.05$, °° or ** – $p < 0.01$, °°° or *** – $p < 0.001$; # – $p < 0.05$ – differences between LKhT 6-19 and mexidol at similar doses are significant (Fisher's exact test).

The effect of new nicotinic acid derivatives on the model of amnesia in mice induced by acute hypoxia in the hermetic chamber

It was demonstrated that the majority (71%, $p < 0.001$) of mice had retrograde amnesia of CPAR 24 h after the 13–15-min stay of the animals in the hermetic chamber (Table 4).

LKhT 4-19 at doses of 25 and 50 mg/kg did not significantly affect amnesia of CPAR and at a dose of 100 mg/kg significantly weakened the amnesic effect by 2.7 times ($p < 0.01$).

LKhT 6-19 as in the two previous models of amnesia was efficient in all three tested doses. Thus, it significantly ($p < 0.01$) reduced the severity of amnesia at a dose of 25 mg/kg by 3.4 times and at doses of 50 and 100 mg/kg completely prevented its development.

LKhT 7-19 at doses of 25 and 50 mg/kg did not significantly affect amnesia of CPAR and at a dose of 100 mg/kg significantly ($p < 0.05$) weakened the amnesic effect by 2.0 times.

Two other new compounds, LKhT 9-19 and LKhT 13-19 (25, 50, and 100 mg/kg), were inefficient.

The reference drug mexidol had the antiamnestic activity at doses of 50 and 100 mg/kg, almost completely or completely preventing the development of amnesia, and at a dose of 25 mg/kg it did not significantly affect amnesia severity.

In terms of the intensity of the antiamnestic effect, LKhT 6-19 at a dose of 25 mg/kg significantly ($p < 0.05$) exceeded mexidol at a similar dose by 2.5 times, acting as mexidol at a dose of 50 mg/kg, whereas at a dose of 50 mg/kg it acted as mexidol at a dose of 100 mg/kg.

Therefore, three of the five new nicotinic acid derivatives, LKhT 4-19 (100 mg/kg), LKhT 6-19 (25, 50, and 100 mg/kg), and LKhT 7-19 (100 mg/kg), exhibit the antiamnestic properties on the model of amnesia induced by acute hypoxia in a hermetic chamber. At the same time, the most efficient substance LKhT 6-19 exceeds mexidol by the intensity of the action.

Our results obtained on the antiamnestic activity in new nicotinic acid derivatives are indirectly confirmed by the literature data. For example, it was shown that the new Russian drug ampasse (calcium salt of N-(5-hydroxy-nicotinoyl)-L-glutamic acid) at a dose of 5–20 mg/kg had the antiamnestic properties on models of amnesia induced by ECS or scopolamine in rats (Kiselev et al. 2011). It was found that on the model of amnesia in mice induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, the early nicotinamide administration (2–12 h after amnesic exposure) was able to reduce the severity of memory disorders. However, the delayed administration of nicotinamide resulted in decreased effects (Yang et al. 2004).

It was also shown that 1-methylnicotinamide known as the main metabolite of nicotinamide, with intragastric administration at 100 or 200 mg/kg for 3 weeks significantly reversed the bilateral intrahippocampal injection of beta-amyloid $A\beta_{1-42}$-induced or lipopolysaccharide-induced cognitive impairments in mice in the Morris water maze, Y-maze, and Novel object recognition tests. In addition, 1-methylnicotinamide suppressed neuroinflammation, decreased the expression of IL-6, TNF-α and protein of nuclear factor-kappa B p65 (NF-κB p65), and the activation of microglia and astrocytes in the hippocampus and frontal cortex, as well as attenuated neuronal apoptosis (Fu et al. 2019, Mu et al. 2019).

More recently, it was found that nicotinamide mononucleotide (intraperitoneally 100 mg/kg on alternate days for 3 months) can prevent diabetes-induced memory deficits and the loss of CA1 neurons, although it had no significant effect on hyperglycemic control in rats with streptozotocin-induced diabetes (Chandrasekaran et al. 2020).

Nicotinamide mononucleotide (100 mg/kg for 28 every other day) alleviates aging-induced memory impairment in rats of 24 months old (Hosseini et al. 2019).

The results from animal and human interventional studies and epidemiological research suggest that nicotinamide may be beneficial in preserving and enhancing the neurocognitive functions (Rennie et al. 2015). The presence of nootropic activity not only in nicotinamide, but also in its structural analogues was previously reported (Akhundov et al. 1990).

As for drugs created on the basis of nicotinic acid, as far back as a few decades ago picamilon (nicotinoyl gamma-aminobutyric acid) was found to have the antiamnestic properties on various models of amnesia in animals (Voronina et al. 1987). Moreover, it was found in clinical studies involving patients with hypertensive dyscirculatory encephalopathy that the inclusion of picamilon in complex therapy contributed to the improvement of cognitive activity (Povetkin et al. 2009).

Under the similar experimental conditions, it was shown that the calcium channel blocker nimodipine, a derivative of pyridindicarboxylic acid close to nicotinic acid, had the antiamnestic properties on the model of ESC-induced amnesia in rats (Zupan et al. 1996).

Conclusion

To conclude, three of the five new nicotinic acid derivatives, LKhT 4-19 (100 mg/kg), LKhT 6-19 (25, 50, and 100 mg/kg), and LKhT 7-19 (100 mg/kg), have the antiamnestic properties on the models of amnesia in mice induced by ESC, scopolamine, and acute hypoxia in a hermetic chamber. At the same time, the most efficient substance – LKhT 6-19 – exceeds the reference drug mexidol in terms of the intensity of its action on all the models used. In addition, the latter is also more efficient than the two other new compounds, LKhT 4-19 and LKhT 7-19, on the model of ESC-induced amnesia and LKhT 7-19 on the scopolamine-induced amnesia model.

Therefore, LKhT 6-19 is promising for further advanced preclinical studies as a potential drug with antiamnestic activity.

Conflict of interest

Authors declare no conflict of interest.

References

- Akhundov RA, Zagorevskiĭ VA, Voronina TA (1990) Nootropic activity of nicotinamide and its structural analogs. Bulletin of Experimental Biology and Medicine [Biulleten' Eksperimental'noĭ Biologii i Meditsiny] 110(10): 384–386. https://doi.org/10.1007/BF00842287 [PubMed] [in Russian]
- Belskaya GN, Chuprina SE, Vorobyev AA, Gorozha EN, Butorakina TL, Sokolov MA, Izmaylov IA (2016) Cognitive disorders in stroke patients: the possibilities of pharmacological correction. S.S. Korsakov Journal of Neurology and Psychiatry [Zhurnal Nevrologii i Psikhiatrii im. S.S. Korsakova] 116(5): 33–37. https://doi.org/10.17116/jnevro20161165133-37 [in Russian]
- Bogolepova AN, Levin OS (2020) Cognitive rehabilitation of patients with focal brain damage. S.S. Korsakov Journal of Neurology and Psychiatry [Zhurnal Nevrologii i Psikhiatrii im. S.S. Korsakova] 120(4): 115–122. https://doi.org/10.17116/jnevro2020120041115 [PubMed] [in Russian]
- Chandrasekaran K, Choi J, Arvas MI, Salimian M, Singh S, Xu S, Gullapalli RP, Kristian T, Russell JW (2020) Nicotinamide mononucleotide administration prevents experimental diabetes-induced cognitive impairment and loss of hippocampal neurons. International Journal of Molecular Sciences 21(11): 3756. https://doi.org/10.3390/ijms21113756 [PubMed] [PMC]
- Cumin R, Bandle EF, Gamzu E, Haefely WE (1982) Effects of the novel compound aniracetam (Ro 13-5057) upon impaired learning and memory in rodents. Psychopharmacology 78(2): 104–111. https://doi.org/10.1007/BF00432244 [PubMed]
- Frantellizzi V, Conte M, De Vincentis G (2021) Hybrid imaging of vascular cognitive impairment. Seminars in Nuclear Medicine 51(3): 286–295. https://doi.org/10.1053/j.semnuclmed.2020.12.006 [PubMed]
- Fu L, Liu C, Chen L, Lv Y, Meng G, Hu M, Long Y, Hong H, Tang S (2019) Protective effects of 1-methylnicotinamide on Aβ $_{1-42}$-induced cognitive deficits, neuroinflammation and apoptosis in mice. Journal of Neuroimmune Pharmacology: the official journal of the Society on NeuroImmune Pharmacology 14(3): 401–412. https://doi.org/10.1007/s11481-018-09830-1 [PubMed]
- Gasperi V, Sibilano M, Savini I, Catani MV (2019) Niacin in the central nervous system: an update of biological aspects and clinical applications. International Journal of Molecular Sciences 20(4): 974. https://doi.org/10.3390/ijms20040974 [PubMed] [PMC]
- Hosseini L, Farokhi-Sisakht F, Badalzadeh R, Khabbaz A, Mahmoudi J, Sadigh-Eteghad S (2019) Nicotinamide mononucleotide and melatonin alleviate aging-induced cognitive impairment via modulation of mitochondrial function and apoptosis in the prefrontal cortex and hippocampus. Neuroscience 423: 29–37. https://doi.org/10.1016/j.neuroscience.2019.09.037 [PubMed]
- Kiselev AV, Stovbun SV, Sergienko VI (2011) Study of the nootropic effects of D- and L-isomers of N-(5-hydroxynicotinoyl)-glutamic acid. Bulletin of the Moscow State Regional University. Series: Natural Sciences [Vestnik Moskovskogo Gosudarstvennogo Oblastnogo Universiteta. Seriya: Estestvennye Nauki] 2: 47–49. [in Russian]
- Kotov SV, Isakova EV, Zaitseva EV, Egorova YuV (2020) Multimodal stimulation in the neurorehabilitation of patients with post-stroke cognitive impairment. S.S. Korsakov Journal of Neurology and Psychiatry [Zhurnal Nevrologii i Psikhiatrii im. S.S. Korsakova] 120(5): 125–130. https://doi.org/10.17116/jnevro2020120051125 [PubMed] [in Russian]
- Kulesh AA, Shestakov VV (2016) Post-stroke cognitive impairment and the possibility of treatment with cellex. S.S. Korsakov Jour-

nal of Neurology and Psychiatry [Zhurnal Nevrologii i Psikhiatrii im. S.S. Korsakova] 116(5): 38–42. https://doi.org/10.17116/jnevro20161165138-42 [PubMed] [in Russian]
- Mendelson SJ, Prabhakaran S (2021) Diagnosis and management of transient ischemic attack and acute ischemic stroke: a review. JAMA 325(11): 1088–1098. https://doi.org/10.1001/jama.2020.26867 [PubMed]
- Miners S, Kehoe PG, Love S (2020) Cognitive impact of COVID-19: looking beyond the short term. Alzheimer's Research & Therapy 12(1): 170. https://doi.org/10.1186/s13195-020-00744-w [PubMed] [PMC]
- Mondadori C, Bhatnagar A, Borkovski J, Häusler A (1990) Involvement of a steroidal component in the mechanism of action of piracetam-like nootropics. Brain Research 506(1): 101–108. https://doi.org/10.1016/0006-8993(90)91204-T [PubMed]
- Mu RH, Tan YZ, Fu LL, Nazmul Islam M, Hu M, Hong H, Tang SS (2019) 1-Methylnicotinamide attenuates lipopolysaccharide-induced cognitive deficits via targeting neuroinflammation and neuronal apoptosis. International Immunopharmacology 77: 105918. https://doi.org/10.1016/j.intimp.2019.105918 [PubMed]
- Parfenov VA (2019) Poststroke cognitive impairment. Neurology, Neuropsychiatry, Psychosomatics [Nevrologia, Nejropsikhiatria, Psikhosomatika] 11(4): 22–27. https://doi.org/10.14412/2074-2711-2019-4-22-27 [in Russian]
- Povetkin SV, Laskov VB, Chernyshkov EV (2009) The influence of cavinton forte and picamilone on cognitive disorders in patients with dyscirculatory encephalopathy. Clinical Gerontology [Klinicheskaya Gerontologiya] 10–11: 17–21. [in Russian]
- Putaala J (2020) Ischemic stroke in young adults. Continuum (Minneapolis Minnesota) 26(2): 386–414. https://doi.org/10.1212/CON.0000000000000833 [PubMed]
- Rennie G, Chen AC, Dhillon H, Vardy J, Damian DL (2015) Nicotinamide and neurocognitive function. Nutritional Neuroscience 18(5): 193–200. https://doi.org/10.1179/1476830514Y.0000000112 [PubMed]
- Sharma A, Madan N (2019) Role of niacin in current clinical practice. Minerva Medica 110(1): 79–83. https://doi.org/10.23736/S0026-4806.18.05826-3 [PubMed]
- Skvortsova VI, Shetova IM, Kakorina EP, Kamkin EG, Boiko EL, Alekyan BG, Ivanova GE, Shamalov NA, Dashyan VG, Krylov VV (2018) Results of implementation of a "Complex of measures to improve medical care for patients with stroke in the Russian Federation. S.S. Korsakov Journal of Neurology and Psychiatry [Zhurnal Nevrologii i Psikhiatrii im. S.S. Korsakova] 118(4): 5–12. https://doi.org/10.17116/jnevro2018118415-12 [PubMed] [in Russian]
- Stakhovskaya LV, Kotov SV (2018) Stroke: a Guide for Doctors [Insul't: Rukovodstvo dlya Vrachei]. Medical Information Agency, Moscow, 487 pp. [in Russian]
- Sun MK (2018) Potential therapeutics for vascular cognitive impairment and dementia. Current Neuropharmacology 16(7): 1036–1044. https://doi.org/10.2174/1570159X15666171016164734 [PubMed]
- Tabeeva GR (2019a) Neurocognitive aging and cognitive disorders. S.S. Korsakov Journal of Neurology and Psychiatry [Zhurnal Nevrologii i Psikhiatrii im. S.S. Korsakova] 119(6): 160–167. https://doi.org/10.17116/jnevro2019119061160 [PubMed] [in Russian]
- Tabeeva GR (2019b) Mild cognitive impairment: what's next? S.S. Korsakov Journal of Neurology and Psychiatry [Zhurnal Nevrologii i Psikhiatrii im. S.S. Korsakova] 119(10): 103–110. https://doi.org/10.17116/jnevro2019119101103 [PubMed] [in Russian]
- Van der Flier WM, Skoog I, Schneider JA, Pantoni L, Mok V, Chen CLH, Scheltens P (2018) Vascular cognitive impairment. Nature Reviews. Disease Primers 4: 18003. https://doi.org/10.1038/nrdp.2018.3 [PubMed]
- Voronina TA, Garibova TL, Khromova IV, Tilekeeva UM (1987) Dissociation of the anti-amnesic and antihypoxic effects of nootropic and antihypoxic preparations. Pharmacology and Toxicology [Farmakologiia i Toksikologiia] 50(3): 21–24. [PubMed] [in Russian]
- Voronina TA, Ostrovskaya RU, Garibova TL (2012) Methodological recommendations for the preclinical study of drugs with a nootropic type of action [Metodicheskie Rekomendatsii po Doklinicheskomu Izucheniyu Lekarstvennyh Sredstv s Nootropnym Tipom Dejstviya.]. In: Mironov AN, Bunyatyan ND, Vasiliev AN, Verstakova OL, Zhuravleva MV, Lepakhin VK, Uteshev DB, Korobov NV, Merkulov VA, Orekhov SN, Sakaeva IV, Uteshev DB, Yavorskij AN (Eds) Guidelines for Preclinical Studies of Drugs [Rukovodstvo po Provedeniyu Doklinicheskikh Issledovaniy Lekarstvennykh Sredstv] Part 1. Grif and K, Moscow, 276–296. [in Russian]
- Voronina TA (2016) The pioneer of antioxidant neuroprotection. 20 years in clinical practice. Russian Medical Journal [Russkiy Meditsinskiy Zhurnal] 24(7): 434–438. [in Russian]
- Yang J, He L, Wang J, Adams Jr JD (2004) Early administration of nicotinamide prevents learning and memory impairment in mice induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine. Pharmacology, Biochemistry, and Behavior 78(1): 179–183. https://doi.org/10.1016/j.pbb.2004.03.007 [PubMed]
- Yasnetsov VikV, Kaurova DE, Bersenev EYu, Skachilova SYa (2020) Investigation of the antihypoxic properties of new nicotinic acid derivatives. Aerospace and Environmental Medicine [Aviakosmicheskaya i Ekologicheskaya Meditsina] 54(5): 73–76. https://doi.org/10.21687/0233-528X-2020-54-5-73-76 [in Russian]
- Zupan G, Vitezić D, Mrsić J, Matesić D, Simonić A (1996) Effects of nimodipine, felodipine and amlodipine on electroconvulsive shock-induced amnesia in the rat. European Journal of Pharmacology 310(2–3): 103–106. https://doi.org/10.1016/0014-2999(96)00534-1 [PubMed]

Author contributions

- **Victor V. Yasnetsov,** Doctor Habil. of Medical Sciences, Chief Researcher, Laboratory of Pharmacology, All-Union Research Center for Safety of Biologically Active Substances; Leading Researcher, Laboratory of Experimental and Clinical Pharmacology, State Scientific Center of Russian Federation – Institute of Biomedical Problems of the Russian Academy of Sciences, e-mail: vicyas@yandex.ru, **ORCID ID** https://orcid.org/0000-0002-6399-3703. The author developed the idea, concept and design of the study, took part in experimental work and wrote the initial draft.

- **Diana E. Kaurova,** postgraduate student, specialist in educational and methodological work, Resource Center for Teacher Education of Moscow Region, e-mail: berseneva_diana@mail.ru, **ORCID ID** https://orcid.org/0000-0002-6261-9832. The author developed the idea, concept and design of the study, conducted the experiments and statistic processing of the obtained data and prepared the final version of the article.

- **Sofia Ya. Skachilova,** Doctor Habil. of Chemical Sciences, Professor, Head of Department, Department of Chemistry and Technology of Synthetic Drugs and Analytical Control, e-mail: skachilova@mail.ru, **ORCID ID** https://orcid.org/0000-0003-4486-8883. The author carried out the synthesis of the studied compounds and provided consulting support.

- **Evgeniy Yu. Bersenev,** PhD in Biology, Leading Researcher, Laboratory of Vegetative Regulation of the Cardiovascular System; Deputy Head, Department of Physiology and Biomechanics of the Cardiorespiratory System in Extreme Condition, e-mail: bersenev_evgenii@mail.ru, **ORCID ID** https://orcid.org/0000-0002-6974-5196. The author took part in experimental work and conducted the statistic processing of the obtained data.