AN IMPACT OF BETA-PHENYLGLUTAMIC ACID HYDROCHLORIDE (A COMPOUND OF RGPU-135, NEUROGLUTAME) IN VARIOUS DOSES UPON COGNITIVE FUNCTIONS OF ANIMALS

Tyurenkov I.N., Bagmetova V.V., Chernysheva Y.V., Merkushenkova O.V.

Volgograd State Medical University, Volgograd, e-mail: vvbagmetova@gmail.com

Hydrochloric of beta-phenylglutamine acid (RGPU-135, glutarone) in its wide range of doses from 13 to 130 mg/kg increases latent period of the first entrance to a dark cell within the test «conditional reaction of passive avoidance» among animals. At the same time it repeats the reflex after 14 days of its producing and decreases latent period of diving within the «test of extrapolative escape», this skill reproduces after 24 hours and 14 days of training – nootropic characteristics are displayed. Nootropic effect of RGPU-135 compound is mostly expressed in doses of 26 and 52 mg/kg – the solution expresses its basic pharmacological activity, and it can be studied as an additional positive characteristic of a new agent of antidepressant, anxiolytic, and neuroprotective effect that is based on RGPU-135 compound.

Keywords: hydrochloride of beta-phenylglutamine acid, psychotropic agents, nootropics, nootropic effect, cognitive functions

Hydrochloride of beta-phenylgutamine acid (a compound of RGPU-135, glutarone) has a wide range of psychotropic effects [1, 5, 6] and also a low toxicity and potentially high medical safety [2, 3]. Pharmacologists of Volgograd state medical university are developing a new unique psychotropic substance that possesses antidepressant, anxiolytic, and neuroprotective effect at the base of RGPU-135 compound. Apart from well-expressed antidepressant and anxiolytic effects we can outline nootropic component among psychotropic effects of RGPU-135 [5], and it distinguishes the solution positively from the majority of known effective antidepressants and anxiolytics. Thus, many antidepressants express anticholinergic properties of various intensities, and one of their clinic expressions can lead to disturbance of memory and ability to concentrate. Anxiolytics, especially those of benzodiazinic line, combine anxiolytic and sedative effect, and the latter impacts cognitive functions negatively due to general non-specific oppression of central nervous system. Therefore, a presence of nootropic effect within the action range of a potential agent of antidepressant and anxiolytic effect can be considered a positive characteristic that possibly could increase life quality of patients in case such medication was introduced into clinical practice. However, dose ranges, in which basic and additional pharmacological properties of medications are expressed, do not coincide quite often, so, at the stage of pre-clinical research of RGPU-135 compound, comparing dose intervals in which its nootropic effect is expressed with experimentally-proved efficient dose of 26 mg/kg [5], has been considered urgent.

Research goals – studying an impact of beta-phenylgutamine acid hydrochloride in different doses upon cognitive functions of animals.

Materials and methods of research

Experiments have been carried out on outbred male rats (180–220 g) that have been contained in standard vivarium conditions. The research has been carried out according to the Order of Ministry of Healthcare and Social Development of Russian Federation № 708N dated 23.08.2010 «On asserting rules of laboratory practice», GOST R-53434-2009 «Principles of appropriate laboratory practice», rules of European convention on protection of vertebrate animals that are used for experimental and other scientific purposes(1986). Study of RGPU-135 impact upon cognitive functions of animals has been carried out with usage of 6 doses, selected according to the data of their acute toxicity [2, 3] and results of earlier researches [5]. All used doses were multiple to the experimentally-proved therapeutic dose – 26 mg/kg that forms 1/300 of LD_{50} [5]: 13 mg/kg is dose more than two times smaller than therapeutically-effective one, is close to 1/700 of LD_{50} [5]; 52 mg/kg is a two times bigger dose than therapeutically-effective one, it closes to 1/200 of LD_{50}; 78 mg/kg is three times bigger dose than therapeutically-effective one, it closes to 1/100 of LD_{50}; 130 mg/kg is five times bigger dose than therapeutically-effective one, it closes to 1/70 of LD_{50}; 650 mg/kg is twenty-five times bigger dose than therapeutically-effective one, it closes to 1/10 of LD_{50} (it has been studied as subtoxic).

An impact of beta-phenylglutamine acid hydrochloride of various doses upon cognitive functions of animals was studied in a test «conditional reaction of passive avoidance» [4] and the «test of extrapolative escape» [4] with checking of a reflex preservation in 25 hours and 14 days after training. RGPU-135 compound has been dissolved in 2% amylaceous slime, solutions have been prepared ex tempore and introduced to animals once endogastrically (through probe) one hour before training according to the mentioned tests. A control group of animals has been formed as well, 2% amylaceous slime has been introduced to them in equal volume. Statistical processing of the results: ranging unifactorial analysis of Kruskal-Wallis, criterion of Newman-Keuls, exact criterion of Fisher.

Results of research and their discussion

Hydrochloride of beta-phenylglutamine acid has expressed nootropic properties in a wide range of doses from 13 to 130 mg/kg.

It provided for mastering conditional reflex of passive avoidance among animals that expressed in an increase of latent period (LP) of the first entrance into a dark cell with reproducing the reflex on day 14 after the training in comparison to the results of control animals (Table 1). In doses of 26 and 52 mg/kg RGPU-135 compound has led to statistically-significant alterations in this indication and thus expressed maximal nootropic effect.

Table 1

An impact of beta-phenylglutamine acid hydrochloride in various doses upon producing and mastering a reflex in test «conditional reaction of passive avoidance»

Animal group	LP of entering a dark cell, M ± m			Number of animals entered (N/n)		
	Training	Reproduction in 24 hr	Reproduction in 14 days	Training	Reproduction in 24 hr	Reproduction in 14 days
Control	45,13 ± 5,24	162,50 ± 17,50	98,00 ± 31,01	8/8	1/8	4/8
RGPU-135 – 13 mg/kg	53,00 ± 4,65	180,00 ± 0,00	157,75 ± 12,08	8/8	0/8	3/8
RGPU-135 – 26 mg/kg	42,75 ± 4,45	180,00 ± 0,00	171,28 ± 5,68*	8/8	0/8	2/8
RGPU-135 – 52 mg/kg	58,38 ± 4,19	180,00 ± 0,00	167,75 ± 8,71*	8/8	0/8	2/8
RGPU-135 – 78 mg/kg	55,00 ± 4,39	180,00 ± 0,00	151,75 ± 14,08	8/8	0/8	3/8
RGPU-135 – 130 mg/kg	64,25 ± 6,43	180,00 ± 0,00	143,00 ± 20,85	8/8	0/8	3/8
RGPU-135 – 650 mg/kg	73,38 ± 6,76*	179,38 ± 0,63	108,13 ± 18,02	8/8	1/8	4/8

N o t e s : N/n is number of animals in a group (N) that have visited a dark cell of total number of animals in a group (n); * – $p < 0,05$ in comparison to the control group of animals (ranging unifactorial analysis of Kruskal-Wallis, criterion of Newman-Keuls, exact criterion of Fisher).

In the test of «extrapolative escape» beta-phenylglutamine acid hydrochloride has also improved training ability and memory among animals in dose interval from 13 to 130 mg/kg. The improvement reflected in decrease in LP of diving at stages of reflex reproduction in 24 hours and 14 days after the training (Table 2). While using RGPU-153 in doses 26, and less in 52 mg/kg, this effect has been statistically-significant. While introducing subtoxic dose of glutarone of 650 mg/kg to animals, a disturbance in ability to master a skill of extrapolative escape – a statistically-significant increase in LP of diving has been registered at the training stage and at the stage of checking skill preservation in 24 hours and 14 days after training.

Table 2

An impact of beta-phenylglutamine acid hydrochloride in various doses upon producing and mastering a reflex in test «extrapolative escape»

Animal group	Diving LP, M ± m		
	Training	Reproduction in 24 hr	Reproduction in 14 days
Control	49,75 ± 3,27	32,75 ± 2,14	25,50 ± 1,89
RGPU-135 – 13 mg/kg	40,75 ± 5,45	29,63 ± 2,76	22,38 ± 1,60
RGPU-135 – 26 mg/kg	38,75 ± 7,31	24,38 ± 1,66*	17,00 ± 1,10**
RGPU-135 – 52 mg/kg	42,50 ± 5,97	25,88 ± 2,31*	19,88 ± 1,52*
RGPU-135 – 78 mg/kg	43,88 ± 5,57	31,13 ± 2,52	22,00 ± 1,21
RGPU-135 – 130 mg/kg	46,00 ± 3,97	34,75 ± 2,46	27,50 ± 2,63
RGPU-135 – 650 mg/kg	62,50 ± 4,36*	45,50 ± 4,12*	38,88 ± 3,77**

N o t e s : * – $p < 0,05$; ** – $p < 0,01$ in comparison to the control group of animals (ranging unifactorial analysis of Kruskal-Wallis, criterion of Newman-Keuls, exact criterion of Fisher).

Thus, RGPU-135 compound provides for improvement in mastering a conditional reflex of passive avoidance and the skill of extrapolative escape among animals when used in a wide range of doses from 13 to 130 mg/kg that proves the solution's nootropic properties. We should outline that nootropic effect of this compound is mostly expressed in doses of 26 and 52 mg/kg, in which its antidepressive and anxiolytic effect is mostly displayed [1, 5, 6]. Disturbance in training ability and memory in the «test of extrapolative escape» among animals that received subtoxic dose of RGPU compound 650 mg-kg can be a consequence of its toxic impact in this dose, as earlier researches show that clinic of intoxication with this compound goes with oppression of central nervous system.

Conclusion

Hydrochloride of beta-phenylglutamine acid (a compound of RGPU-135, glutarone) in a wide range of doses from 13 to 130 mg/kg (statistically-significant in doses of 26 and 52 mg/kg) increases LP of the first entrance into a dark cell among animals in a test «conditional reaction of passive avoidance», the reflex preserves in 14 days after training, and decrease LP of diving in the «test of extrapolative escape», the skill is reproduced in 24 hours and 14 days after training, thus displaying its nootropic properties. Nootropic effect of RGPU-135 is displayed in doses that provide for its main pharmacologic properties – antidepressant and anxiolytic activity. This property of a new medication of antidepressantm anxiolytic, and neuroprotective effect that is developed on the foundation of RGPU-135 should be considered as an additional effect that could increase life quality of patients in case of introducing this preparation into clinical practice.

References

1. Bagmetova V.V., Chernysheva Yu.V., Merkushenkova O.V. i dr. Sravnitel'naja ocenka antidepressivnyh svojstv gidrohlorida β-fenilglutaminovoj kisloty (RGPU-135, glutaron) // Jeksperimental'naja i klinicheskaja farmakologija. – T. 76. – № 3. – 2013. – P. 7–9.

2. Bugaeva L.I., Tyurenkov I.N., Bagmetova V.V. i dr. Izuchenie ostroj toksichnosti gidrohlorida β–fenilglutaminovoj kisloty pri odnokratnom vnutribrjushinnom vvedenii // Vestnik Volgogradskogo gosudarstvennogo medicinskogo universiteta – 2012. – № 3 (43). – P. 30–33.

3. Bugaeva L.I., Tyurenkov I.N., Bagmetova V.V. i dr. Ostraja toksichnost' substancii gidrohlorida β-fenilglutaminovoj kisloty pri odnokratnom vnutrizheludochnom vvedenii mysham i krysam // Vestnik Volgogradskogo gosudarstvennogo medicinskogo universiteta. – 2012. – № 4. – P. 34–37.

4. Rukovodstvo po provedeniju doklinicheskih issledovanij lekarstvennyh sredstv. Chast' pervaja. – M.: Grif i K, 2012. – 944 p.

5. Sredstvo, obladajushhee antidepressantnym, anksioliticheskim, nejroprotektornym i immunostimulirujushhim dejstviem / Petrov V.I., Tyurenkov I.N., Bagmetova V.V., Samotrueva M.A., Berestovitskaya V.M., Vasilieva O.S., Ostroglyadov E.S. // patent na izobretenie RUS 2429834, 23.07.2010

6. Tyurenkov I.N., Bagmetova V.V., Chernysheva Yu.V. i dr. Sravnenie psihotropnyh svojstv glutaminovoj kisloty i ee novogo proizvodnogo – gidrohlorida beta-fenilglutaminovoj kisloty (RGPU-135, glutarona) // Fundamental'nye issledovanija. – 2013. – № 3 – 1. – P. 167–172.