DOI: 10.26565/2312-5675-2020-15-04
UDC: 615.221: 615.232: 615.036.8: 616.8: 616.08: 616.8: 614.88: 616.24-008.44

CORRECTION OF COGNITIVE-MNESTIC DYSFUNCTION OF RATS AFTER KETAMINE ANESTHESIA UNDER THE INFLUENCE OF HETEROSIDE

I. V. Kabachna, E. V. Suprun, V. I. Kabachnyy, O. O. Mamina

Kabachna Iryna V.N. Karazin Kharkiv National University, Ukraine, 61022, Kharkiv, Svobody Square, 6
dr.kabachnaya@gmail.com
ORCID ID: 0000-0002-5668-4216

Suprun Elina *National University of Pharmacy, Ukraine, 61002, Kharkiv, Pushkinska street, 53
elinasuprun202@gmail.com
ORCID ID: 0000-0003-0199-2948

Kabachnyy Volodymyr* kabachny@nuph.edu.ua
ORCID ID: 0000-0002-6669-2850

Mamina Olena* physcollchem@nuph.edu.ua
ORCID ID: 0000-0001-6673-1488

Today, in medical practice, a very promising direction of development can be the expansion of the range of primary and secondary neuroprotection drugs through the use of targeted synthesis of potential neuroprotective agents with analeptic effect. This is necessary to improve anesthetic safety during surgery and to alleviate post-anesthetic intoxication after anesthesia.

Therefore, the aim of our study was to compare the neuroprotective activity of original derivatives of sulfur and nitrogen-containing heterocycles (heterosides) and reference drugs, which are already known in pharmacology (cerebroprotective agent with neurotrophic action – cerebrocurin and nootropic drug with neuroprotective action – noopept).

In the course of the research, it was found that after ketamine anesthesia, the excitability of the central nervous system increases, the anxious behavior of animals increases, while the indicators of the research work of animals in the experiment sharply deteriorate. After 2 days or more (10 days) after the transferred ketamine anesthesia, a deterioration in mnestic functions was noted in this group of animals.

With the introduction of 100 mg / kg of heteroside to a group of rats after ketamine anesthesia, the indicators of anxiety behavior and excitability of animals significantly decreased, their research activity increased, a pronounced antiamnestic effect was manifested, and the ability of animals to learn was increased as well.

It also turned out that in terms of the degree of influence on the indicators of the cognitive-mnestic functions of the central nervous system, heteroside statistically significantly exceeds the comparison drugs cerebrocurin and noopept, which in turn showed high efficiency in reducing anxiety of animals, and also had an antiamnestic effect, but did not affect the ability of animals to learn.

Key words: heteroside, ketamine, postoperative cognitive dysfunction, neuroprotection, cerebrocurin, noopept, anamnestic effect.

Introduction.

The degree of protection of the body from surgical trauma using various methods of anesthesia, as well as criteria for its adequacy, currently continue to be the one of the main subject of discussion. Previously, it was believed that effects of general anesthesia (GA) occur quickly and same quickly disappear, so after removing anesthetics from the body the brain returns to the preoperative state and patient wakes up, so the negative effects of GA on the central nervous system (CNS) in the post-anesthesia period decrease and disappear. However, in recent years, with the accumulation of data from epidemiological and experimental studies of the effects of GA on the brain, it has become clear that central anesthetics in addition to the main analgetic and hypnogenic effects cause permanent ischemic / hypoxic neuronal and neurological changes and a number of neurotoxic side effects by triggering apoptosis (the programmed death of neurons) [1]. It is shown that the frequency and severity of side effects of anesthesia on the CNS are affected by the dose of anesthetics and the duration of general anesthesia [2; 3].

The earliest manifestation of neuronal damage caused by GA is a violation of higher cortical functions, primarily memory and cognitive processes, and the development of postoperative cognitive dysfunction (PCD) [4]. The most sensitive to the action of general anesthetics are attention function, short-term memory, the speed of psychomotor and cognitive reactions. However, in the literature only some works are devoted to the use of neuroprotective drugs for the prevention and treatment of neurocognitive disorders in the postoperative period [5; 6].

Prophylactic neuroprotective therapy together with the selection of an adequate option of anesthesia, correction of hemodynamic disorders, level of blood gas exchange and homeostasis if necessary, is the most essential way to prevent neuronal damage or eliminate cognitive dysfunction, which has already occurred in the early postoperative period, while this this changes are potentially reversible [7; 8].

In order to improve anesthesial safety during surgery, a promising direction may also be to expand the range of primary and secondary neuroprotection by targeted synthesis of potential neuroprotectors with analeptic action, acting to the same structures, which are ultimately suppressed by the central anesthetic or its active metabolites [5]. In regard to this, it is reasonable and promising to search among the derivatives of sulfur- and nitrogen-containing heterocycles (heterosides) - universal, harmless neuroprotectors with analeptic action, which can quickly and effectively accelerate the resuscitation of vital functions of the body, general detoxification, arrange detoxification and even solve medical and social problems of emergencies [9].

It is justified, that use of the neurotrophic cerebroprotector cerebrocurin (a new generation neuropeptide-containing drug derivate of the cattle embryos) is promising [10], same as noopept - nootropic drug for the correction of postoperative cognitive-mnestic dysfunction. The neuroprotective effect of noopept has a complex mechanism of action. It is capable of counteracting glutamate excitotoxicity in cerebral ischemia, as well as long-term effects of stress factors, mental and emotional stress or intoxication [10].

The aim of the study was to evaluate the neuroprotective effect of heteroside, cerebrocurin and noopept in correction of cognitive-mnestic and behavioral disorders after ketamine anesthesia.

Materials and methods. In the experiments were used white outbred rats weighing 180-200 g, obtained from the nursery of the Institute of Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine. The duration of quarantine (acclimatization period) for all animals was 14 days. All experimental procedures were performed in accordance with the "Regulations on the use of animals in biomedical research."The study was conducted in accordance with Directive 2010 / 63EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, as well as with the national "Common Ethical Principles for Animal Experiments" (Ukraine, 2001) and the guidelines set out in in "Basic principles of studying the toxicity of potential pharmacological drugs" (DFC of Ukraine, K., 2000). The animals were kept on a standard diet of vivarium with a natural change of day and night. Animals had free access to water. The NUPh Bioethics Committee (Protocol № 5/1 dated 17.05.2017) found that conducted research does not contradict the generally accepted bioethical norms on compliance with the relevant international provisions regarding the conduct of experimental research.

The original derivates of sulfur- and nitrogen-containing heterocycles Heteroside-321 was synthesized at the Department of Physical and Colloid Chemistry of the National University of Pharmacy (laboratory sample). During research there were determined the ED50 analeptic activity as 2 mg / kg and LD50 by express method Pastushenko T.V. - 1350 mg / kg, which according to the classification of Hodge and Sterner allowed to classify them as class IV (low toxic substances) [11].

Neuroprotective activity (according to mnestic-behavioral changes) of heteroside-321 and reference drugs as cerebrocurin and noopept was researched on 50 Wistar rats aged 6 months weighing 180-200 grams. Ketamine

anesthesia was performed by intraperitoneal administering 100 mg / kg of ketamine. After releasing of animals from anesthesia, they were once administered drugs in the following doses: Heteroside-321 — intraperitoneal 2 mg / kg, cerebrocurin (LLC "NIR", Ukraine — intraperitoneal 0,2 mg / kg, noopept (CJSC "Masterclone", produced by OJSC "Shcholkivsky vitamin factory") — intranasal 10 mg / kg. The animals were divided into 5 groups, each of it include ten animals. The first group — intact animals (control), the second - animals with experimental ketamine anesthesia (control ketamine pathology — CKP), the third - animals with anesthesia Heteroside-321 (CKP + Heteroside-321 group), fourth and fifth - animals with anesthesia administered Cerebrocurin (CKP + Cerebrokurin group) or Noopept (CKP + Noopept group). Intact group received a single intraperitoneal sodium chloride solution of 1 ml per 100 g of weight. The CKP group after administration of ketamine once received intraperitoneal sodium chloride in a similar dosage (at the same period of time as other 3 groups (CKP + Heteroside-321, CKP + Cerebrokurin, CKP + Noopept) received injections of neuroprotectors) .

Determination of motor and search activity was carried out using the method of "Open Field" using the arena of its own production with size of 80x80x35cm. The animal was placed in the middle of one of two sides face to the wall, after which it was allowed to move free in the arena during 8 minutes. During experiment we counted the total distance which animal traveled (cm), total motor activity (cm^2 / s), activity structure (high, low activity, lack of activity, %), the number of fading and entering the center, the distance traveled near the wall (cm) and in the Central region arena (%), vertical search activity (number of racks on hind legs near the wall and in the center), the number of events of short and long grooming, the number of defecation and urination acts.

Evaluation of reference and working memory was performed using a radial maze LE760 (AgnTho's, Sweden). During studies were counted the reference memory (general long-term understanding of the structure of the maze and the location of food which was formed in animals during training) and the number of errors of the reference memory (first visits to a previously closed beam in which the animal has never found food), as well as working memory (when animal has short-term idea of the location of food in a particular experience) and the number of errors in working memory (re-visiting of the district in which animal has already found or did not find food). The distance traveled and total motor activity were assessed as well. Finding and recording the image was performed using a color video camera SSC-DC378P (Sony, Japan). The video file was analyzed using Smartv 3.0 software (Harvard Apparatus, USA).

The results of the study were calculated using the standard statistical package of the licensed program "STATISTICA® for Windows 6.0" (StatSoftInc., №AXXR712D833214FAN5), as well as "SPSS 16.0", "Microsoft Office Excell 2003". The normality of the distribution was evaluated by the Shapiro-Wilk test. The data are presented as an average value. Significance of differences between mean values was determined by Student's test in the normal distribution. In the case of a distribution other than normal, or analysis of ordinal variables, the U Mann-Whitney test was used. To compare the independent variables in more than two samples, analysis of variance (ANOVA) at normal distribution or Kruskal-Wallis test for distribution other than normal was used. Differences $p < 0.05$ (95%) were considered statistically significant for all types of analysis.

Results and discussion. General anesthesia can cause CNS damage in the postoperative period, among which a special place is occupied by postoperative cognitive dysfunction, which can develop in patients of different ages and in cases with a unencumbered psychoneurological history.

Due to the increase in metabolism and energy expenditure in the conditions of operation under GA, the need of tissues for oxygen increases, but its delivery can be sharply reduced by the lack of microcirculation. Anesthesia changes the acid-base state (ABS) and tissue respiration, and the general absorption of oxygen by the body. The development of neurological complications and the severity of the condition of patients under the influence of general anesthetics depended on the harmful effects of ischemia, which is determined by the depth and duration of the decrease in cerebral blood flow. Tissue hypoxia with decreased oxygen diffusion due to impaired microcirculation, changes in blood rheology and vascular wall leads to dysfunction of different cellular structures, including neurons. The effect of general anesthetics on the human brain is characterized by the fact that they have numerous target actions (different parts of the brain, spinal cord); the action is determined by the physic and chemical properties of the agent; different clinical effects are achieved by acting on different targets (for example, the effect of immobilization and cognitive dysfunction-CD). Therefore, the correction of cognitive-mnestic and behavioral disorders after ketamine anesthesia should be considered as a neuroprotective strategy [12; 13].

During evaluating the specific indicators of the "Open field" test, it was found that ketamine anesthesia negatively affected the behavioral characteristics of animals (Table 1).

After 2 days of ketamine anesthesia injection it was found that it was not lead to a significant increase in the distance traveled by animals, but at same moment there was 8,97 times increased the free distance in absolute units and 11 times increased in a percentage of total motor activity.

Also in results of the control group was found that the number of fading increased 1,86 times and 1,5 times increased the immobility of animals. All these facts indicate

Table 1

Behavioral activity of rats in the "Radial labyrinth" and "Open field" tests

Indicator	Intact Control	Ketamine anesthesia	Ketamine anesthesia + Heteroside	Ketamine anesthesia + Cerebrokurin	Ketamine anesthesia + Noopept
Radial labyrinth test					
General activity,cm2/ s	24380,98±1242,43	26867,58±1543,58	24674,29±1477,601,2^{K}	44862,35±2686,54^{*,K}	34863,66±3082,05*
The number of mistakes in the reference memory	2	3	1*, ^{K}	2^{K}	1*, ^{K}
The number of mistakes of working memory	4±1	13±1^{1}	4±1 $^{K, C, N}$	5±1 ^{K}	2$^{*, K, C}$
Open field test					
Number of occurrences in the center, units	1	2	1±1	1±1	1
High activity,%	7,83±1,44	14,83±2,07*	12,01±0,87$^{*, K, C, N}$	21,83±1,58$^{*, K}$	10,50±1,45$^{K, C}$
Low activity,%	61,71±7,08	65,83±4,03	63,84±2,03^{N}	65,17±3,69	78,30±1,59*, $^{K, C}$
Inactivity,%	30,47±6,59	22,34±4,37	27,15±2,55 $^{K, C, N}$	13,00±4,64*	11,20±0,67^{*,K}
Immobility, units	284±35	429±27*	346,75±11,55$^{*,K,Ц, N}$	85±21^{*,K,N}	138±17^{*,K,C}
Indicator,%	Intact Control	Ketamine anesthesia	Ketamine anesthesia + Heteroside	Ketamine anesthesia + Cerebrokurin	Ketamine anesthesia + Noopept
Free distance, cm	59,37±26,31	529,76±215,98*	178,00±48,79$^{*, K, C, N}$	323,64±88,71*	226,10±33,44 $^{K, N}$
Fading, units	284±35	529±27*	305,70±17,60 $^{K, C, N}$	374±32^{K}	242±28$^{K, N}$
Free distance,%	1,43±0,61	11,30±2,67*	4,91±1,11$^{*, K, C, N}$	8,92±2,011	7,06±1,20$^{*, K, N}$
Distance around the wall, cm	4102,44±289,55	3672,27±612,74	3723,79±154,79 C	2770,53±281,43	3690,16±1105,34
Rack near the wall, units	4±1	8±11	5±1 K	6±1 K	5±1
The rack is free, units	2	2±1	1	1	1±1
Short grooming, units	2±1	1	1	1±1	1
Long-lasting grooming, units	1	1	1	1	1
Defecation, units	3	2	2±1	2	1$^{*, K}$
Urination, units	1±1	1	1	1	2

Notes:

1. * - significant (p <0,05) differences relative to intact animals;
2. ^{K} - significant (p <0,05) differences relative to the control group;
3. ^{C} - significant (p <0,05) differences relative to the group of Cerebrocurin;
4. ^{N} - significant (p <0,05) differences relative to the Noopept group;
5. n is the number of animals in the group.

the formation of anxiety and excitability in animals after ketamine anesthesia. The introduction of ketamine did not affect the number of free racks of animals, but led to a 2-fold increase in racks near the wall.

Also, the number of acts of short grooming decreased 2 times against the background of a constant number of long grooming. This fact showed increasing of anxiety, excitability, irritability of animals, decreasing sense of comfort. In animals of the control group there was a 2-times increasing in high activity, which indicated a high emotionality and excitability of the animals. Increasing in high activity can also be seen as a decreasing in the ability to research and search activities, as the rat makes an excessive number of "extra" movements and requires more time to assimilate the new environment.

During evaluating of specific indicators of training in the radial labyrinth (Table 1), it was found that 10 days after ketamine anesthesia of animals they had cognitive dysfunction. The overall activity of animals in this group had no significant differences with the control group. During reproducing the results of animal training, it was found that on the 10th day after the introduction of ketamine the number of errors in working memory increases by 3,25 times and the number of errors in reference memory by 1,5 times which are indicators of a violation of mnestic functions in animals after ketamine anesthesia. The data obtained by us can be explained with the concept of postoperative cognitive dysfunction.

Ketamine anesthesia leads to the formation of persistent cognitive deficiency, as well as psycho-emotional disorders - inhibition, fear, anxiety, disorientation, aggression and irritability. The use of ketamine in the elderly may impair the oligomerisation and deposition of amyloid beta protein and thus cause long-term cognitive effects.

One of the main causes of cognitive impairment after surgery is considered to be the neurotoxic effect of ketamine, which leads to inhibition of glutamate transmission, inhibition of synaptogenesis, depletion of synapse energy balance and disruption of neurotransmitter reuptake mechanisms, as well as initiation of circulatory and animal excretion mechanisms of circulatory ischemia [14]. Injection of neurotropic drugs – Heteroside-321, noopept and cerebrocurin in time of awakening animals from anesthesia differently affected behavioral responses, increasing of emotional status and cognitive-mnestic functions of animals.

Administration of cerebrocurin to animals after ketamine had a beneficial effect on the emotional status and behavior of animals in the open field after ketamine anesthesia. Thus, cerebrocurin reduced anxiety and excitability, as evidenced by a significant reduction in free space, the number of fades and racks near the wall. At the same time cerebrocurin did not affect the comfort of animals (grooming, defecation). Cerebrocurin reduced immobility by 5 times, which can also be regarded as the anxiolytic effect of the drug.

At the same time cerebrocurin leads to an increase in high activity (1,8 times compared to intact and 1,7 times compared to control) and reduced inactivity (2,3 times compared to intact and 1,7 times compared to control), which can be regarded as a decrease in the ability to research activity and increase the excitability of animals. Cerebrocurin significantly (2,6 times) reduced the number of errors in working memory and the amount of reference memory (1,5 times) for 10 days after ketamine anesthesia.

The injection of noopept to animals after ketamine anesthesia led to a decrease in anxiety, fear and excitability (reduction of free space by 2,3 times, fading by 2,2 times, racks near the wall by 1,6 times and immobility by 3 times compared to control). According to these indicators, noopept significantly exceeds both the value of the control group and the value of cerebrocurin.

After injection of the Heteroside-321 there was an increase in free distance of 10,4 compared with the intact group and 1,16 times compared with the control. The introduction of Heteroside-321 did not reduce the number of fading (1,4 times higher than the intact value) and inactivity. The number of racks near the wall under the action of Heteroside-321 (1,75 times) remains higher than intact, and the number of acts of short grooming remains at the level of control (2 below intact), and low (1,5 times) remains the number defecation. These facts suggest that the Heteroside-321 reduces anxiety, fear, excitability and discomfort in animals for 2 days after ketamine anesthesia. Heteroside-321 also had a positive effect on the indicators of cognitive-mnestic functions, because on the 10th day after ketamine anesthesia, the errors of working and reference memory were reduced.

Conclusions:

1. Ketamine anesthesia leads to increase anxiety behavior of animals, excitability (increased duration of inactivity and the number of cases of fading, increased free space visiting, the number of racks near the wall, reduced grooming and defecation), deterioration of research and exploration activity for 2 days and more (10 days) leads to deterioration of mnestic functions (increase in the number of errors of the reference and working memory).

2. Parenteral injection of cerebrocurin and noopept to animals after ketamine anesthesia significantly reduced the anxiety of animals, and also had an anti-amnestic effect

(significant reduction of working memory errors), but did not affect the ability of animals to learn.

3. The infusion of Heteroside-321 to animals after ketamine anesthesia significantly reduced the indicators of anxiety and excitability of animals (reduction of the number of fading and inactivity, free space, racks near the wall), increased research activity, showed a high anamnestic effect (reduction of errors of reference and working memory) increased the ability of animals to learn (decrease high and increase low activity). In terms of the degree of influence on the indicators of cognitive-mnestic functions of the CNS, the Heteroside-321 is significantly more effective in comparison to the neuroprotective drugs cerebrocurin and noopept.

The authors declare no conflicts of interest.

REFERENCES

1. M. Perouansky, H. C. Hemmings. Neurotoxicity of general anesthetics. Anesthesiology. 2009, vol. 111, no 6, pp. 1365-1371.

2. G. Micha, P. Tzimas, I. Zalonis et al. Propofol vs Sevoflurane anaesthesia on postoperativecognitive dysfunction in the elderly. A randomized controlled trial. Acta Anaesthesiol Belg. 2016, no. 67 (3), pp. 129-137.

3. Zhong X. Mood and neuropsychological effects of different doses of ketamine in electroconvulsive therapy for treatment-resistant depression. J Affect Disord. 2016, no. 39.201, pp. 124-130.

4. A. Borozdina, E. Qeva, M. Cinicola, F. Bilotta. Perioperative cognitive evaluation. Curr Opin Anaesthesiol. 2018, no. 31 (6), pp. 756-761.

5. B. Wang, S. Ge, W. Xiong, Z. Xue. Effects of resveratrol pretreatment on endoplasmic reticulum stress and cognitive function after surgery in aged mice. BMC Anesthesiol. 2018, no. 18 (1), pp. 141-147.

6. F. Hovaguimian, C. Tschopp, B. Beck-Schimmer, M. Puhan. Intraoperative ketamine administration to prevent delirium or postoperative cognitive dysfunction: A systematic review and meta-analysis. Acta Anaesthesiol Scand. 2018, no. 62 (9), pp. 1182-1193.

7. G.I. Gubina-Vakulik, U. A. Fesenko, V. V. Myasodov. Morphological assessment of ketamine and neuroprotective powers of piracetam and magnesium sulfate on hipocampal neurons in schurivs. Ukrainian morphological almanac. 2009, vol. 7, no. 4, pp. 29-34. [in Ukr.]

8. Radtke F. M. Monitoring depth of anesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth. 2013, no. 110 (suppl. 1), pp. 98-105.

9. I. Kabachna, E. Suprun, V. Kabachnyy. Mechanisms of analeptic and antigipoxic effects of heterosides - derivatives for sulfur and nitrogen containing heterocycles. World Science. 2018, vol. 1, no. 12 (40), pp. 29-34.

10. I. S. Chekman, I. F. Belenichev, L. A. Gromov et al. Preclinical study of the specific activity of potential neuroprotective drugs: Method. recommendations of the State Pharmaceutical Center of the Ministry of Health of Ukraine. Kiev: Avicenna. 2016, 80 p. [in Russ.]

11. I. V. Kabachna, S. M. Drogovoz, V. I. Kabachnyy, N. Yu. Palagina. Pre-treatment of analeptic activity of the childish sircote of nitrogen heterocycles on the model of ketamine anesthesia. Pharmacology and toxicology. 2017, no. 4-5 (55), pp. 27-32. [in Ukr.]

12. J. W. Olney, J. Labruyere, M. T. Price. W. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. Science. 1989, no. 244, pp. 1360-1362.

13. Li Xinran, Yanan Li, Jinghua Zhao et al. Administration of Ketamine Causes Autophagy and Apoptosis in the Rat Fetal Hippocampus and in PC12. Cells. Front Cell Neuroscience. 2018, no. 12, pp. 21-29.

14. C. Scallet, R. Divine, C. Wang et al. Ketamine-induced neurotoxicity in prenatal rhesus monkeys: distribution of neuronal damage. Social Neuroscience Abstracts. 2005, no. 251, pp. 15-23.

ЛІТЕРАТУРА

1. Perouansky M. Neurotoxicity of general anesthetics / M. Perouansky, H. C. Hemmings // Anesthesiology. - 2009. - Vol. 111, No. 6. - P. 1365-1371.

2. Propofol vs Sevoflurane anesthesia on postoperative cognitive dysfunction in the elderly. A randomized controlled trial / G. Micha, P. Tzimas, I. Zalonis [et al.] // Acta Anesthesiol Belg. - 2016. - Vol. 67 (3). - P. 129-137.

3. Zhong X. Mood and neuropsychological effects of different doses of ketamine in electroconvulsive therapy for treatment-resistant depression / X. Zhong // J Affect Disord. - 2016. - Sep 1, Vol. 39.201 .- P. 124-130.

4. Borozdina A. Perioperative cognitive evaluation / A. Borozdina, E. Qeva, M. Cinicola, F. Bilotta // Current Opinion in Anesthesiology. - 2018. - Dec, Vol. 31 (6). - P. 756-761.

5. Wang B. Effects of resveratrol pretreatment on endoplasmic reticulum stress and cognitive function after surgery in aged mice / B. Wang, S. Ge, W. Xiong, Z. Xue // BMC Anesthesiol. - 2018. - Oct 10, Vol. 18 (1). - P. 141-147.

6. Hovaguimian F. Intraoperative ketamine administration to prevent delirium or postoperative cognitive dysfunction: A systematic review and meta-analysis / F. Hovaguimian, C. Tschopp, B. Beck-Schimmer, M. Puhan // Acta Anaesthesiol Scand. - 2018. - Oct, Vol. 62 (9). - P. 1182-1193.

7. Губіна-Вакулік Г. І. Морфологічна оцінка дії кетаміну та нейропротективних властивостей пірацетаму та сульфату магнію на нейрони гіпокампа у щурів / Г. І. Губіна-Вакулік, У. А. Фесенко, В. В. М'ясоєдов // Український морфологічний альманах. – 2009. – Т. 7, № 4. – С. 29-34.

8. Radtke F. M. Monitoring depth of anesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction / F. M. Radtke // Br J Anaesth. – 2013. – Vol. 110 (Suppl. 1). – P. 98-105.

9. Kabachna I. Mechanisms of analeptic and antigipoxic effects of heterosides – derivatives for sulfur and nitrogen containing heterocycles / I. Kabachna, E. Suprun, V. Kabachnyy // World Science. – 2018. – Vol. 1, № 12 (40). – P. 29-34.

10. Чекман И. С. Доклиническое изучение специфической активности потенциальных нейропротективных препаратов: Метод. рекомендации ГФЦ МЗ Украины / И. С. Чекман, И. Ф. Беленичев, Л. А. Громов и [др.] // Киев: Авиценна, 2016. – 80 с.

11. Кабачна І. В. Дослідження аналептичної активності похідних сірко- та азотвмісних гетероциклів на моделі кетамінового наркозу / І. В. Кабачна, С. М. Дроговоз, В. І. Кабачний, Н. Ю. Палагіна // Фармакологія та лікарська токсикологія. – 2017. – № 4-5 (55). – С. 27-32.

12. Olney J. W. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs / J. W. Olney, J. Labruyere, M. T. Price // Science. – 1989. – Vol. 244. – P. 1360-1362.

13. Xinran Li Administration of Ketamine Causes Autophagy and Apoptosis in the Rat Fetal Hippocampus and in PC12 / Li Xinran, Yanan Li, Jinghua Zhao [et al.] // Cells. Front Cell Neuroscience. – 2018. – Vol. 12. – P. 21-29.

14. Scallet A. C. Ketamine-induced neurotoxicity in prenatal rhesus monkeys: distribution of neuronal damage / A. C. Scallet, R. Divine, C. Wang [et al.] // Social Neuroscience Abstracts. – 2005. – Vol. 251. – P. 15-23.

КОРЕКЦІЯ КОГНІТИВНО-МНЕСТИЧНОЇ ДИСФУНКЦІЇ У ЩУРІВ ПІСЛЯ КЕТАМІНОВОГО НАРКОЗУ ПІД ВПЛИВОМ ГЕТЕРОЗИДУ

Кабачна Ірина Володимирівна
Харківський національний університет імені В. Н. Каразіна, Україна, 61022, м. Харків, майдан Свободи, 6
dr.kabachnaya@gmail.com
ORCID ID: 0000-0002-5668-4216

Супрун Еліна Владиславівна
*Національний фармацевтичний університет, Україна, 61002, м. Харків, вул. Пушкінська, 53
elinasuprun202@gmail.com
ORCID ID: 0000-0003-0199-2948

Кабачний Володимир Іванович*
kabachny@nuph.edu.ua
ORCID ID: 0000-0002-6669-2850

Мамина Олена Олександрівна*
physcollchem@nuph.edu.ua
ORCID ID: 0000-0001-6673-1488

На сьогоднішній день в медичній практиці досить перспективним напрямком розвитку може стати розширення асортименту засобів первинної та вторинної нейропротекции шляхом застосування цілеспрямованого синтезу потенційних нейропротекторів з аналептичною дією. Це необхідно для поліпшення анестезіологічної безпеки під час оперативних втручань і полегшення постнаркозної інтоксикації після перенесеної анестезії.

Тому метою нашого дослідження було порівняння нейропротективної активності оригінальних похідних сіро і азотовмісних гетероциклів (гетерозидів) і вже відомих в фармакології референс-препаратів (церебропротектору з нейротрофічною дією – цереброкурину та ноотропного препарату з нейропротективною дією – ноопепту).

В ході проведення досліджень було встановлено, що після кетамінової анестезії зростає збудливість ЦНС, посилюється тривожна поведінка тварин, при цьому показники дослідницької роботи тварин в експерименті різко погіршуються. Через 2 дні і більше (10 днів) після перенесеного кетамінового наркозу відзначалося погіршення мнестичних функцій в цій групі тварин.

При введенні 100 мг / кг гетерозиду групі щурів після кетамінової анестезії достовірно знижувалися показники тривожної поведінки і збудливості тварин, зростала їх дослідницька активність, проявлявся виражений антиамнестичний ефект і підвищувалася здатність тварин до навчання.

Також виявилося, що за ступенем впливу на показники когнітивно-мнестичних функцій ЦНС гетерозид статистично достовірно перевершує препарати порівняння цереброкурін і ноопепт, які в свою чергу показали високу ефективність у зниженні тривожності тварин, а також надавали антиамнестичний ефект, але при цьому не впливали на здатність тварин до навчання.

Ключові слова: гетерозид, кетамін, післяопераційна когнітивна дисфункція, нейропротекція, цереброкурин, ноопепт, антиамнестичний ефект.

КОРРЕКЦИЯ КОГНИТИВНО-МНЕСТИЧЕСКОЙ ДИСФУНКЦИИ У КРЫС ПОСЛЕ КЕТАМИНОВОГО НАРКОЗА ПОД ВЛИЯНИЕМ ГЕТЕРОЗИДА

Кабачная Ирина Владимировна Харьковский национальный университет имени В. Н. Каразина, Украина, 61022, г. Харьков, площадь Свободы, 6
dr.kabachnaya@gmail.com
ORCID ID: 0000-0002-5668-4216

Супрун Элина Владиславовна *Национальний фармацевтический университет, Украина, 61002, г. Харков, ул. Пушкинская, 53
elinasuprun202@gmail.com
ORCID ID: 0000-0003-0199-2948

Кабачный Владимир Иванович* kabachny@nuph.edu.ua
ORCID ID: 0000-0002-6669-2850

Мамина Елена Александровна* physcollchem@nuph.edu.ua
ORCID ID: 0000-0001-6673-1488

На сегодняшний день в медицинской практике весьма перспективным направлением развития может стать расширение ассортимента средств первичной и вторичной нейропротекции путем применения целенаправленного синтеза потенциальных нейропротекторов с аналептическим действием. Это необходимо для улучшения анестезиологической безопасности во время оперативных вмешательств и облегчения постнаркозной интоксикации после перенесенной анестезии.

Поэтому целью нашего исследования было сравнение нейропротективной активности оригинальных производных серо- и азотсодержащих гетероциклов (гетерозидов) и уже известных в фармакологии референс-препаратов (церебропротектора с нейротрофическим действием – цереброкурина и ноотропного препарата с нейропротективным действием – ноопепта).

В ходе проведения исследований было установлено, что после кетаминовой анестезии растет возбудимость ЦНС, усиливается тревожное поведение животных, при этом показатели исследовательской работы животных в эксперименте резко ухудшаются. Через 2 дня и более (10 дней) после перенесенного кетаминового наркоза отмечалось ухудшение мнестических функций в этой группе животных.

При введении 100 мг/кг гетерозида группе крыс после кетаминовой анестезии достоверно снижались показатели тревожного поведения и возбудимости животных, возрастала их исследовательская активность, проявлялся выраженный антиамнестический эффект и повышалась способность животных к обучению.

Также оказалось, что по степени влияния на показатели когнитивно-мнестических функций ЦНС гетерозид статистически достоверно превосходит препараты сравнения цереброкурин и ноопепт, которые в свою очередь показали высокую эффективность в снижении тревожности животных, а также оказывали антиамнестический эффект, но при этом не влияли на способность животных к обучению.

Ключевые слова: гетерозиды, кетамин, послеоперационная когнитивная дисфункция, нейропротекция, цереброкурин, ноопепт, антиамнестический эффект.