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Kisspeptins Kiss1 and Kiss2 in fish modulate corticoliberin and gonadoliberin gene expression in brain structures of *Danio rerio*

Aleksey V. Lizunov, Aleksandra A. Blazhenko, Aleksey S. Komlev, Polina E. Petrova, Platon P. Khokhlov, Eugeny R. Bychkov, Petr D. Shabanov

Institute of Experimental Medicine, Saint Petersburg, Russia

ABSTRACT

BACKGROUND: The kisspeptin system in the brain is crucial for regulating reproductive functions in humans and animals. In contrast to mammals, the brains of *Danio rerio* express two types of kisspeptins, Kiss1 and Kiss2. The role of these kisspeptins in hormonal regulation in fish remains an important area of investigation.

AIM: To examine the effects of Kiss1 and Kiss2 on corticoliberin and gonadoliberin gene expression in the midbrain and diencephalon of *Danio rerio*.

MATERIALS AND METHODS: Kisspeptins Kiss1 and Kiss2 are oligopeptides consisting of 13 and 9 amino acid residues, respectively. *Danio rerio* fish were administered intracerebroventricular injections of 1 ng and 4 ng of each peptide at 1 µL volumes. At 1 and 4 hours post-administration, the fish brains were extracted, and the midbrain and diencephalon were isolated as a single complex. Gene expression levels of corticoliberin and gonadoliberin were analyzed using real-time polymerase chain reaction (PCR).

RESULTS: Intracerebroventricular administration of Kiss1 and Kiss2 significantly modulated corticoliberin and gonadoliberin gene expression in the midbrain and diencephalon of *Danio rerio*. In the group injected with 4 ng of Kiss1, *corticoliberin* gene expression increased 17- and 65-fold after 4 hours compared to the control groups. In the group administered 1 ng of Kiss2, *corticoliberin* gene expression increased by 23- and 92-fold compared to the control groups after 1 hour. In the group administered 4 ng of Kiss1, *gonadoliberin* gene expression decreased threefold compared to the control group euthanized at 1 hour. In the group administered 1 ng of Kiss2, *gonadoliberin* gene expression decreased fourfold compared to the control group after 1 hour. In the group administered 1 ng of Kiss2, *gonadoliberin* gene expression decreased threefold compared to the control group after 4 hours.

CONCLUSION: The experimental results reveal that Kiss1 and Kiss2 kisspeptins in *Danio rerio* stimulate corticoliberin gene expression while suppressing gonadoliberin gene expression in the midbrain and diencephalon.

Keywords: Danio rerio; Kiss1; Kiss2; corticoliberin; gonadoliberin.

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Кисспептины рыб Kiss1 и Kiss2 модулируют экспрессию генов кортиколиберина и гонадолиберина в структурах головного мозга *Danio rerio*

А.В. Лизунов, А.А. Блаженко, А.С. Комлев, П.Е. Петрова, П.П. Хохлов, Е.Р. Бычков, П.Д. Шабанов

Институт экспериментальной медицины, Санкт-Петербург, Россия

АННОТАЦИЯ

Актуальность. Кисспептиновая система мозга играет важную роль в регуляции репродуктивной функции человека и животных. В отличие от млекопитающих в мозге рыб *Danio rerio* экспрессируется 2 типа кисспептинов — Kiss1 и Kiss2. Актуальным является вопрос о роли кисспептинов в гормональной регуляции у рыб.

Цель. Изучить влияние Kiss1 и Kiss2 на экспрессию генов кортиколиберина и гонадолиберина в среднем и промежуточном мозге у *Danio rerio*.

Материалы и методы. Кисспептины Kiss1 и Kiss2 представляют собой олигопептиды длиной 13 и 9 аминокислотных остатков соответственно. Рыбам *Danio rerio* интрацереброventрикулярно вводили 1 и 4 нг каждого пептида в объеме 1 мкл. Через 1 и 4 ч после введения олигопептидов, у рыб извлекали головной мозг, выделяли средний и промежуточный мозг единым комплексом и исследовали экспрессию генов кортиколиберина и гонадолиберина с помощью полимеразной цепной реакции в режиме реального времени.

Результаты. При интрацереброventрикулярном введение кисспептинов Kiss1 и Kiss2 отмечена модуляция экспрессия генов кортиколиберина и гонадолиберина в структурах среднего и промежуточного мозга *Danio rerio*. В группе, которой вводили Kiss1 в дозе 4 нг, через 4 ч экспрессия гена *Corticoliberin* повысилась по сравнению с контрольными группами в 17 и 65 раз. В группе, которой вводили Kiss2 в дозе 1 нг, через 1 ч экспрессия гена *Corticoliberin* повысилась по сравнению с контрольными группами в 23 и 92 раза. В группе, которой вводили Kiss1 в концентрации 4 нг, через 1 ч экспрессия гена *Gonadoliberin* понизилась в 3 раза по сравнению с контрольной группой, забитой через 1 час. В группе, которой вводили Kiss2 в концентрации 1 нг, через 1 ч экспрессия гена *Gonadoliberin* понизилась по сравнению с контрольной группой в 4 раза. В группе, которой вводили Kiss2 в концентрации 1 нг, через 4 ч экспрессия гена *Gonadoliberin* понизилась по сравнению с контрольной группой в 3 раза.

Заключение. Проведенные экспериментальные исследования свидетельствуют о том, что введение кисспептинов костистых рыб Kiss1 и Kiss2 приводит к активации гена кортиколиберина и подавлению активности гена гонадолиберина в структурах головного мозга рыб *Danio rerio.*

Ключевые слова: Danio rerio; Kiss1; Kiss2; кортиколиберин; гонадолиберин.

Как цитировать
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BACKGROUND

The kisspeptin system in the brain is crucial for regulating reproductive functions in humans and animals. Kisspeptin activates the hypothalamic-pituitary-gonadal (HPG) axis by stimulating the secretion of gonadotropin-releasing hormone (GnRH) in the hypothalamus [1]. In humans, the *Kiss1* gene encodes a 145-amino-acid protein. The active forms of kisspeptin are short peptides containing 54, 14, 13, and 10 amino acid residues, which bind to the kisspeptin receptor KISS1R.

The zebrafish (*Danio rerio*) is widely used as a model organism to evaluate the pharmacological activity of new compounds. In contrast to mammals, the brain of *Danio rerio* expresses two types of kisspeptins—Kiss1 and Kiss2. Kiss1 in fish is an ortholog of mammalian Kiss1; however, it does not regulate gonadal function but rather suppresses fear responses and promotes exploratory behavior [2]. At the same time, the Kiss2 peptide is involved in the regulation of reproductive function in fish and is synthesized in the periventricular region of the hypothalamus. Administration of Kiss2, but not Kiss1, increased the expression of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) genes in the pituitary gland of female *Danio rerio* [3].

GnRH is synthesized in the hypothalamus and stimulates the release of FSH and LH from the anterior pituitary gland. GnRH activity is also linked to sexual and social behavior in fish. Studies have shown that cichlids with elevated GnRH expression display a greater tendency for dominant behavior [1, 4]. In humans, GnRH is encoded by the *GNRH1* gene, whereas in *Danio rerio*, it is encoded by the *gnrh*3 gene.

Corticotropin-releasing hormone (CRH) regulates the activity of the hypothalamic-pituitary-adrenal (HPA) axis. CRH stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. It is primarily synthesized in the paraventricular nucleus of the hypothalamus and is encoded by the *CRH* gene in humans and the *crh* gene in *Danio rerio*. CRH plays a key role in the stress response and is one of the primary triggers of anxiety, fear, and distress, which contribute to reduced appetite, sleep disturbances, and decreased sexual activity. Strong morphofunctional connections have been observed between corticotropin-releasing hormone-containing and kisspeptinergic neurons. One of the first studies investigating the influence of the HPA axis on kisspeptin suggested that both acute and chronic stress reduce kisspeptin levels, thereby suppressing the synthesis and secretion of pituitary LH [1, 5, 6].

AIM: To investigate the effects of intracerebroventricular administration of fish kisspeptins Kiss1 and Kiss2 in *Danio rerio* on the expression of gonadotropin-releasing hormone and corticotropin-releasing hormone genes in the midbrain and diencephalon.

MATERIALS AND METHODS

The selection of experimental animals (*Danio rerio*) and their housing conditions have been previously described in detail [7]. Anesthesia and sample collection from the midbrain and diencephalon were performed according to standard protocols [8].

Danio rerio kisspeptins Kiss1 (NVAYYNLNSFGLRY-NH_2) and Kiss2 (FNYNPFGLRF-NH_2) were synthesized using the standard Fmoc-based solid-phase peptide synthesis method at the Department of General Pathology and Pathophysiology, Federal State Budgetary Scientific Institution, Institute of Experimental Medicine (St. Petersburg) [9].

The animals were divided into ten groups: Group 1 (Control 1), intracerebroventricular (ICV) injection of 1 µL saline, euthanized 1 hour post-injection; Group 2 (Control 2), ICV injection of 1 µL saline, euthanized 4 hours post-injection; Group 3 (Kiss1, 1 ng, 1 µg/mL, 1 hour), ICV injection of 1 ng Kiss1, euthanized 1 hour post-injection; Group 4 (Kiss1, 1 ng, 1 µg/mL, 4 hours), ICV injection of 1 ng Kiss1, euthanized 4 hours post-injection; Group 5 (Kiss1, 4 ng, 4 µg/mL, 1 hour), ICV injection of 4 ng Kiss1, euthanized 1 hour post-injection; Group 6 (Kiss1, 4 ng, 4 µg/mL, 4 hours), ICV injection of 4 ng Kiss1, euthanized 4 hours post-injection; Group 7 (Kiss2, 1 ng, 1 µg/mL, 1 hour), ICV injection of 1 ng Kiss2, euthanized 1 hour post-injection; Group 8 (Kiss2, 1 ng, 1 µg/mL, 4 hours), ICV injection of 1 ng Kiss2, euthanized 4 hours post-injection; Group 9 (Kiss2, 4 ng, 4 µg/mL, 1 hour), ICV injection of 4 ng Kiss2, euthanized 1 hour post-injection; Group 10 (Kiss2, 4 ng, 4 µg/mL, 4 hours), ICV injection of 4 ng Kiss2, euthanized 4 hours post-injection. All intracerebral injections were performed in a total volume of 1 µL.

To assess the expression of corticoliberin and gonadoliberin genes, the fish brains were extracted 1 and 4 hours after Kiss1 and Kiss2 administration. The midbrain and diencephalon were isolated as a single unit, and total mRNA was extracted using a standard protocol. The dissected brain tissue was homogenized in 100 µL of TRIzol reagent and incubated for 5 minutes at 40 °C. Then, 40 µL of chloroform was added to each sample, mixed thoroughly, and incubated for 5 minutes with gentle agitation. The samples were centrifuged at 13,000 g for 10 minutes, and the upper phase was collected. An equal volume of isopropanol was added to the collected upper phase, mixed, and incubated at –20 °C for 24 hours. The samples were then centrifuged at 13,000 g for 10 minutes to collect the pellet. Isopropanol was removed, the pellet was washed with 70% ethanol, dried in a thermal block at 40 °C, and resuspended in 50 µL of deionized water containing 1% RNase inhibitor. After mRNA extraction, reverse transcription reactions were performed. Real-time PCR was then performed using primers specific to the mRNA of corticotropin-releasing hormone (*corticoliberin*, JN859047.1) and gonadotropin-releasing hormone (*gonadoliberin*, AJ304429.1). The reference housekeeping genes used were *cyclophilin* and *glyceraldehyde-3-phosphate*

dehydrogenase (*gapdh*). The expression levels of corticoliberin and gonadoliberin genes were normalized to the geometric mean of the two reference genes (cyclophilin and gapdh) and calculated as relative expression values compared to the control groups.

Statistical analyses were performed using GraphPad PRISM 8.0. The Kolmogorov–Smirnov test was used to assess the normality of data distribution. If the data followed a normal distribution, one-way ANOVA was applied, followed by Tukey's post hoc test for pairwise comparisons between experimental groups. If the data distribution was non-normal or unknown, the Kruskal–Wallis test was performed, followed by Dunn's post hoc test for multiple comparisons. Differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

The mRNA expression levels of the *corticoliberin* gene in the midbrain and diencephalon of *Danio rerio* exhibited the following patterns. In the control group (CG) sampled 1 hour after injection, *corticoliberin* gene expression was four times higher than in the CG sampled 4 hours after saline administration. In Group 3, 1 hour post-injection, *corticoliberin* expression was lower than in the CG (4 hours). In Groups 4 and 5, *corticoliberin* expression did not significantly differ from either CG at the 1-hour time point. In Group 6, *corticoliberin* expression increased 17-fold and 65-fold compared to both CGs after 4 hours. In Group 7, 1 hour post-injection, *corticoliberin* expression increased 23-fold and 92-fold compared to both CGs. In Group 8, after 4 hours, *corticoliberin* expression increased 17-fold and 64-fold compared to both CGs. In Group 9, 1 hour post-injection, *corticoliberin* expression increased 41-fold and 167-fold compared to both CGs. In Group 10, 4 hours post-injection, *corticoliberin* expression increased 19-fold and 75-fold compared to both CGs. These data are presented in Figure 1.

The mRNA expression levels of the *gonadoliberin* gene in the midbrain and diencephalon of *Danio rerio* showed the following results. In the CG sampled 1 hour after saline administration, *gonadoliberin* gene expression was three times higher than in the CG sampled after 4 hours. In groups that received ICV injections of Kiss1 and Kiss2 at a concentration of 1 ng, *gonadoliberin* expression did not significantly differ from either CG at the 1-hour or 4-hour time points. In the group that received an ICV injection of Kiss1 at a concentration of 4 μg/mL, *gonadoliberin* expression decreased threefold compared to the CG sampled at 1 hour. In Group 6, 4 hours post-injection, *gonadoliberin* expression decreased 1.2-fold compared to the CG sampled at 1 hour. In Group 7, after 1 hour, *gonadoliberin* expression decreased fourfold compared to the CG sampled at 1 hour. In Group 8, after 4 hours, *gonadoliberin* expression decreased threefold compared to the CG sampled at 4 hours. In Group 9, after 1 hour, *gonadoliberin* expression decreased threefold compared to the CG sampled at 1 hour. In Group 10, after 4 hours, *gonadoliberin* expression decreased 2.4-fold compared to the CG sampled at 4 hours. These data are presented in Figure 2.

Previous behavioral experiments have demonstrated that various types of stress induce anxiety-like behavior in bony fish [2]. It has been established that this is associated with increased levels of CRH and GnRH in the brain of the studied animals [2, 11]. The regulation of peptide synthesis occurs both at the level of gene expression and at the post-translational level. Therefore, when investigating the mechanisms of action of drugs that alleviate stress-related conditions, it is essential to study changes in the expression levels of stress-related peptide genes. Kisspeptin-based drugs have previously been investigated as anti-stress agents [12]. The present study demonstrated that administration of the Kiss2 peptide in *Danio rerio* increased the expression of the corticoliberin gene while simultaneously decreasing the expression of the gonadoliberin gene in the brain of the studied fish. In contrast, the Kiss1 peptide significantly affected the upregulation of corticoliberin and the downregulation of gonadoliberin gene only at higher concentrations and longer exposure times. This suggests that different kisspeptins activate distinct signaling pathways in neural cells, leading to differential regulation of target genes. Previous studies have shown that CRH plays a key role in the stress-induced anxiety response [6]. Additionally, it has been demonstrated that GnRH is involved in activating reproductive and territorial behaviors in fish, which are linked to stress [4]. Therefore, a compound that activates the corticoliberin gene simultaneously represses the gonadoliberin gene in the brain of *Danio rerio*. It is worth

Table 1. Primer Sequence

Таблица 1. Последовательность праймеров

Gene	Primer sequences	
	Forward (5'-3')	Reverse (3'-5')
Cyclophilin	AGCATCCGCAAACGGAAAAG	CCCTTGTAGCCATAGCCAGG
Gapdh	GATACACGGAGCACCAGGTT	GCCATCAGGTCACATACACG
Corticoliberin	GGTAACGGGATCCTGAGCAG	ATGATCTTGCGGTTGTGGGT
Gonadoliberin	CACTGGTCATACGGTTGGCT	GCAAACCTTCAGCATCCACC

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noting that this effect at the cellular signaling level may arise from the interaction of different kisspeptins with various components of the signaling cascade. The opposing effects on the expression of *corticoliberin* and *gonadoliberin* genes are consistent with previous research findings [13, 14]. Multiple studies have demonstrated that regulatory pathways through signaling cascades in humans and other animal species may function in entirely opposite directions [15, 16]. Consequently, in human cell culture experiments, unlike in fish, the regulation of *CRH* and *GNRH1* gene expression by kisspeptin drugs may be co-directional rather than opposing.

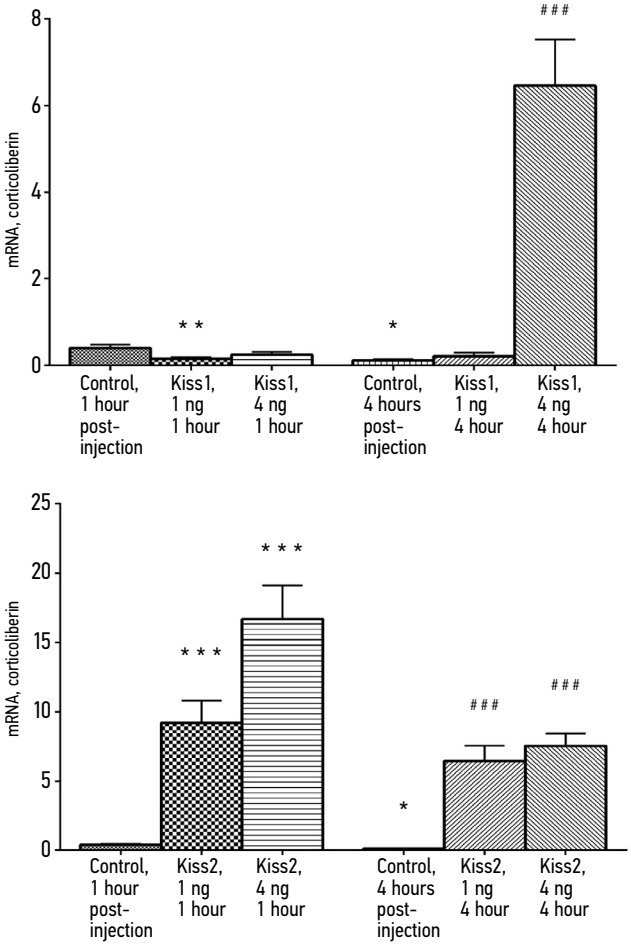

Fig. 1. Corticoliberin gene expression in the midbrain and diencephalon of *Danio rerio*. * — $p < 0.05$, *** — $p < 0.001$ relative to the control group euthanized after 1 hour; ### — $p < 0.001$ relative to the control group euthanized after 4 hours. Data are presented in arbitrary units normalized to the expression levels of *Cyclophilin* and *Gapdh* genes and calculated relative to the mean *corticoliberin* expression in the groups. The alignment was performed using the geometric mean of the reference genes (*Cyclophilin* and *Gapdh*). Data are presented as mean ± standard error of the mean (*M* ± *SEM*)

Рис. 1. Экспрессия гена кортиколиберина в среднем и промежуточном мозге *Danio rerio*. * — $p < 0,05$, *** — $p < 0,001$ по отношению к группе контроля, забитой через 1 час; ### — $p < 0,001$ по отношению к группе контроля, забитой через 4 часа. Данные выражены в условных единицах и нормированы к уровню экспрессии генов циклофилина (*Cyclophilin*) и глицеральдегид-3-фосфатдегидрогеназы (*Gapdh*) и рассчитаны в относительных единицах по отношению к средней величине экспрессии гена *Corticoliberin* в группах. Выравнивание производилось по среднему геометрическому двух референсных генов (*Cyclophilin* и *Gapdh*). Данные представлены как среднее ± стандартная ошибка среднего

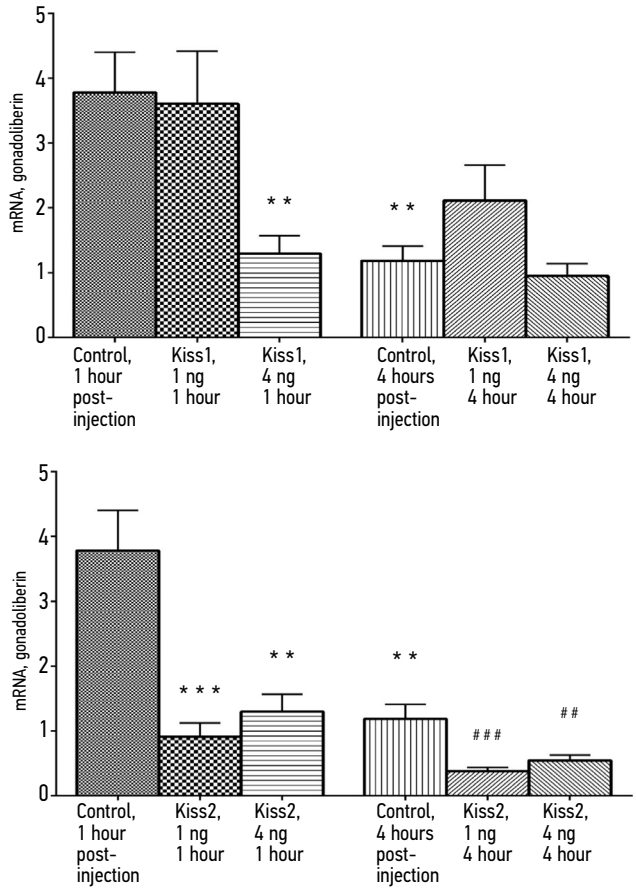

Fig. 2. Gonadoliberin gene expression in the midbrain and diencephalon of *Danio rerio*. ** — $p < 0.01$, *** — $p < 0.001$ relative to the control group euthanized after 1 hour; ## — $p < 0.01$, ### — $p < 0.001$ relative to the control group euthanized after 4 hours. Data are presented in arbitrary units normalized to the expression levels of *Cyclophilin* and *Gapdh* genes and calculated relative to the mean *gonadoliberin* expression in the groups. The alignment was performed using the geometric mean of the reference genes (*Cyclophilin* and *Gapdh*). Data are presented as mean ± standard error of the mean (*M* ± *SEM*)

Рис. 2. Экспрессия гена гонадолиберина в среднем и промежуточном мозге *Danio rerio*. ** — $p < 0,01$, *** — $p < 0,001$ по отношению к группе контроля, забитой через 1 ч; ## — $p < 0,01$, ### — $p < 0,001$ по отношению к группе контроля, забитой через 4 ч. Данные выражены в условных единицах и нормированы к уровню экспрессии генов циклофилина (*Cyclophilin*) и глицеральдегид-3-фосфатдегидрогеназы (*Gapdh*) и рассчитаны в относительных единицах по отношению к средней величине экспрессии гена *Gonadoliberin* в группах. Выравнивание производилось по среднему геометрическому двух референсных генов (*Cyclophilin* и *Gapdh*). Данные представлены как среднее ± стандартная ошибка среднего

CONCLUSION

The obtained data expand current understanding of the mechanisms of action of kisspeptin-based drugs and suggest their potential for further investigation as anti-stress agents.

ADDITIONAL INFORMATION

Author contributions. All authors made significant contributions to concept development, study activities, and preparation of the article, and read and approved the final version before publication. Contribution of each author: A.V. Lizunov — conducting RT-PCR experiments, A.A. Blazhenko — conducting experiments on intracerebral administration of drugs, dissecting animals, A.S. Komlev, P.E. Petrova — data analysis, P.P. Khokhlov — development of the general concept, writing the article, E.R. Bychkov — data analysis, article writing, P.D. Shabanov — development of the general concept.

Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest related to the publication of this article.

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AUTHORS INFO

***Aleksey V. Lizunov,** Cand. Sci. (Biology),
Institute of Experimental Medicine;
address: Russia, 197022, Saint Petersburg, Academician Pavlov st., 12; ORCID: 0000-0001-6458-5683;
e-mail: izya12005@yandex.ru

Alexandra A. Blazhenko, Cand. Sci. (Biology);
ORCID: 0000-0002-8079-0991; eLibrary eLibrary SPIN: 8762-3604;
e-mail: alexandrablazhenko@gmail.com

Aleksey S. Komlev, ORCID: 0000-0001-9111-0755;
eLibrary SPIN: 5921-6703

Polina E. Petrova, ORCID: 0000-0002-9138-8076

Platon P. Khokhlov, Cand. Sci. (Biology);
ORCID: 0000-0001-6553-9267; eLibrary SPIN: 8673-7417;
e-mail: platonkh@list.ru

Eugenii R. Bychkov, Cand. Sci. (Medicine);
ORCID: 0000-0002-8911-6805; eLibrary SPIN: 9408-0799;
e-mail: bychkov@mail.ru

Petr D. Shabanov, MD, Dr. Sci. (Medicine), professor;
ORCID: 0000-0003-1464-1127; eLibrary SPIN: 8974-7477;
e-mail: pdshabanov@mail.ru

ОБ АВТОРАХ

***Алексей Владимирович Лизунов,** канд. биол. наук,
Институт экспериментальной медицины;
адрес: Россия, Санкт-Петербург, 197022, ул. Академика Павлова, 12; ORCID: 0000-0001-6458-5683;
e-mail: izya12005@yandex.ru

Александра Александровна Блаженко, канд. биол. наук;
ORCID: 0000-0002-8079-0991; eLibrary SPIN 8762-3604;
e-mail: alexandrablazhenko@gmail.com

Алексей Сергеевич Комлев, ORCID: 0000-0001-9111-0755;
eLibrary SPIN: 5921-6703

Полина Евгеньевна Петрова, ORCID: 0000-0002-9138-8076

Платон Платонович Хохлов, канд. биол. наук;
ORCID: 0000-0001-6553-9267; eLibrary SPIN: 8673-7417;
e-mail: platonkh@list.ru

Евгений Рудольфович Бычков, канд. мед. наук;
ORCID: 0000-0002-8911-6805; eLibrary SPIN: 9408-0799;
e-mail: bychkov@mail.ru

Петр Дмитриевич Шабанов, д-р мед. наук, профессор;
ORCID: 0000-0003-1464-1127; eLibrary SPIN: 8974-7477;
e-mail: pdshabanov@mail.ru

* Corresponding author / Автор, ответственный за переписку