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Обзоры

А.О. Дробинцева, Т.С. Клейменова, Е.Г. Богомолова, П.М. Копейкин
Кисспептины и их синтетические аналоги: строение, механизм действия и перспективы клинического применения 7

В.О. Еркудов, В.В. Гайворонская, Н.В. Скребцова, С.С. Rogozin
Задержка роста, дефицит питания и микроэлементная недостаточность во Вьетнаме. Часть 2. (Литературный обзор исследований во Вьетнаме). 18

Е.Е. Нужнова, Ю.В. Васильев
Применение максимально недействующей концентрации как аналога индекса биологического воздействия для превентивного мониторинга здоровья работников химической отрасли 49

С.С. Пюрвеев, А.С. Оськина, С.В. Уланова
Трансляционные модели на животных в исследовании регуляции стрессового ответа и сложных механизмов действия глюкокортикоидов. 58

ИННОВАЦИОННАЯ ФАРМАКОЛОГИЯ

Оригинальные статьи

Г.В. Придворов, В.П. Ганопольский, А.А. Спасов
Сравнительная характеристика новых производных бензимидазола с потенциальными анальгетическими свойствами 84

С.С. Пюрвеев, М.С. Некрасов, Г.П. Косякова, В.А. Лебедев, А.Ю. Юров, Т.Е. Лебедева, В.В. Русановский, А.А. Лебедев
Агрелакс снижает условную реакцию предпочтения места этанола и компульсивное поведение крыс на фоне его отмены 93

З.М. Муружева, А.В. Васильева, Д.А. Обухова, О.Н. Эргашев, М.Н. Карпенко, Т.М. Алексеева
Метформин как препарат для адъювантной терапии заболеваний центральной нервной системы 102

НОВЫЕ ТЕХНОЛОГИИ В МЕДИЦИНЕ

Обзоры

К.Ю. Череповский
Методы исследования стопы: традиционные и цифровые технологии (обзор литературы). 116

А.А. Кучай, А.Н. Липин, К.Л. Козлов, Н.Н. Груздев, И.Д. Димов, А.Г. Борисов
Значение и принципы применения эндоваскулярных технологий и «гибридных подходов» в лечении окклюзионных поражений артерий нижних конечностей 125

Н.Н. Груздев, А.В. Антропов, А.Н. Липин, А.А. Кучай, А.Г. Борисов, К.А. Ахмадзас, И.М. Хохлова, Я.П. Эминов, А.И. Любимова
Применение методики гидравлического разрыва Fracking при хронической кальцинированной окклюзии общей бедренной артерии 140

CONTENTS

PATHOPHYSIOLOGY — MEDICINE

Reviews

A.O. Drobintseva, T.S. Kleimenova, E.G. Bogomolova, P.M. Kopeikin
Kisspeptins and their synthetic analogues: structure, mechanism of action and prospects for clinical use. 7

V.O. Erkudov, V.V. Gaivoronskaya, N.V. Screbtsova, S.S. Rogozin
Stunning, malnutrition and microelement deficiency in Vietnam. Part 2. (Literature review of research in Vietnam). 18

E.E. Nuzhnova, Yu.V. Vasiliev
The usage of the maximum inactive concentration as an analogue of the biological impact index for preventive health monitoring of chemical industry workers 49

S.S. Pyurveev, A.S. Oskina, S.V. Ulanova
Translational animal models in the study of stress response regulation and complex mechanisms of glucocorticoid action . . . 58

INNOVATIVE PHARMACOLOGY

Original articles

G.V. Pridvorov, V.P. Ganapolsky, A.A. Spasov
Comparative characteristics of new benzimidazole derivatives with potential analgesic properties 84

S.S. Pyurveev, M.S. Nekrasov, G.P. Kosyakova, V.A. Lebedev, A.Yu. Yurov, T.E. Lebedeva, V.V. Rusanovsky, A.A. Lebedev
Agrelax reduces conditioned place preference of ethanol and compulsive behavior in rats during its withdrawal 93

Z.M. Muruzheva, A.V. Vasilieva, D.A. Obukhova, O.N. Ergashev, M.N. Karpenko, T.M. Alekseeva
Metformin as an adjuvant therapeutic agent in central nervous system disorders. 102

NEW TECHNOLOGIES IN MEDICINE

Reviews

K.Yu. Cherepovsky
Foot examination methods: traditional and digital technologies (literature review). 116

A.A. Kuchay, A.N. Lipin, K.L. Kozlov, N.N. Gruzdev, I.D. Dimov, A.G. Borisov
The importance and principles of endovascular technologies and “hybrid approaches” in the treatment of occlusive lesions of lower extremity arteries 125

N.N. Gruzdev, A.V. Antropov, A.N. Lipin, A.A. Kuchay, A.G. Borisov, K.A. Atmadzas, I.M. Khokhlova, Ya.P. Eminov, A.I. Lubimova
Application of the Fracking hydraulic rupture technique in chronic calcified occlusion of the common femoral artery 140

**ИЗ ИСТОРИИ МЕДИЦИНЫ****Персоналии***А.Н. Зубрицкий*Александр Владимирович Иванов — выдающийся русский
офтальмолог-патолог 149**ИНФОРМАЦИЯ**

Правила для авторов 155

HISTORY OF MEDICINE**Personalities***A.N. Zubritsky*Alexander Vladimirovich Ivanov — outstanding Russian
ophthalmologist-pathologist 149**INFORMATION**

Rules for authors 155



Review

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Kisspeptins and their synthetic analogues: structure, mechanism of action and prospects for clinical use

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ABSTRACT. The literature review compares native kisspeptin (KP) and its synthetic analogues, including modifications that improve its stability in the human body, and characterizes the possibility of their therapeutic use in the correction of reproductive disorders. KP is a key neuropeptide that regulates reproductive function through activation of the *KISS1R* receptor and stimulation of gonadotropin-releasing hormone (GnRH) secretion. It was found that kisspeptin-10 and kisspeptin-54 have different pharmacokinetics, but KP-10 activates the *KISS1R* receptor no less effectively. The mechanism of action of CP is associated with the activation of the Gq/11 protein cascade, leading to an increase in intracellular calcium and activation of phospholipase C. Modifications of kisspeptins that improve their stability are described, including the replacement of amino acids, the addition of protective groups that slow down degradation and can significantly increase the half-life of the peptide in the blood. The main areas of application of kisspeptins in clinical practice, including in the treatment of reproductive disorders and oncology, are considered. Synthetic analogues of kisspeptin, especially those modified to improve stability, are of significant interest for the development of new therapeutic strategies in the field of reproductive medicine. Synthetic analogs of KP that are resistant to degradation by matrix metalloproteinases (MMP-2/9) are being developed. Phosphine analogs that inhibit MMP and prolong the half-life are promising.

Keywords: kisspeptins, kisspeptin receptor agonist, synthetic analogues, G-protein coupled receptors, impairment of reproductive function

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Обзор

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Кисспептины и их синтетические аналоги: строение, механизм действия и перспективы клинического применения

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РЕЗЮМЕ. В литературном обзоре проведено сравнение нативного кисспептина (КП) и его синтетических аналогов, в том числе с модификациями, улучшающими его стабильность в организме человека, и охарактеризованы возможности их терапевтического применения в коррекции нарушений репродуктивной функции. КП представляет собой ключевой нейрорепептид, регулирующий репродуктивную функцию через активацию рецептора *KISS1R* и стимуляцию секреции гонадотропин-рилизинг гормона (ГнРГ). Установлено, что кисспептин-10 и кисспептин-54 обладают различной фармакокинетикой, однако КП-10 не менее эффективно активирует рецептор *KISS1R*. Механизм действия КП связан с активацией Gq/11-белкового каскада, приводящей к повышению внутриклеточного кальция и активации фосфолипазы C. Описаны модификации кисспептинов, улучшающие их стабильность, в том числе замена аминокислот, добавление защитных групп, которые замедляют деградацию и смогут значительно увеличить период полужизни пептида в крови. Рассмотрены основные области применения кисспептинов в клинической практике, в том числе в лечении нарушений репродуктивной функции: при гипогонадотропном гипогонадизме, бесплодии, задержке полового созревания, гормонозависимых опухолях и онкологии. Синтетические аналоги кисспептина, особенно те, что модифицированы для улучшения стабильности, представляют значительный интерес для разработки новых терапевтических стратегий в области репродуктивной медицины. Разрабатываются синтетические аналоги КП, устойчивые к деградации матриксными металлопротеиназами (ММП-2/9). Перспективны фосфиновые аналоги, ингибирующие ММП и продлевающие период полувыведения.

Ключевые слова: кисспептины, агонист рецептора к кисспептинам, синтетические аналоги, рецепторы, сопряженные с G-белком, нарушение репродуктивной функции

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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Kisspeptin (KP) was first discovered in 1996 [1]. mRNA was isolated from the tissue of non-metastatic melanoma, although it was not found in the tissue of metastatic tumors. This discovery highlighted kisspeptin's ability to inhibit metastasis, which led to its original name, metastin [2].

During the study of the *KISS1* gene, it was found that its transcript encodes a hydrophobic protein consisting of 145 amino acids. This protein undergoes proteolytic cleavage, resulting in peptides with a lower molecular weight, known as kisspeptins-54, -14, -13, -10, which have biological activity. The main role of kisspeptins is to control reproductive function in both sexes, and they have been shown to influence the pulsatile release of gonadotropin-releasing hormone (GnRH) in the hypothalamus [3]. In addition, many researchers have established the inhibitory property of KP on cell motility, proliferation, invasion, chemotaxis, and metastasis of tumor cells [4].

Kisspeptin peptides are characterized by variability in different species, but the C-terminus, consisting of 10 amino acids and responsible for binding to the kisspeptin receptor, *KISS1R* (GPR54 in animals), is conserved in both vertebrates and invertebrates [5]. Kisspeptin-10 (KP-10) is a C-terminal fragment with amino acids 45 to 54: Tyr-Asn-Trp-Asn-Ser-Phe-Gly-Leu-Arg-Phe-NH₂, and it is the shortest fragment capable of binding to the kisspeptin receptor with activation of the latter. The action of the 10-amino acid fragment *in vitro* is comparable to the action of the full-length 54-member polypeptide [6, 7].

Kisspeptin is mainly produced in the hypothalamus [8]. KP is synthesized in peripheral organs as well. These include the gonads, brain, pancreas, liver, small intestine, aorta, coronary arteries, and umbilical cord veins [9, 10].

It has been established that the *KISS1* and *KISS1R* genes play a role in the processes of aging, menopause, adipocyte function, and the molecular link between metabolic and reproductive processes, and may act as targets for estrogen [11, 12].

It has been found that the expression of the *KISS1* gene inhibits the activity of matrix metalloproteinases, which is a key mechanism through which *KISS1* prevents tumor metastasis. This process may also play an important role in trophoblast invasion, placental development, and perhaps gestosis [13–15].

KISS1R receptor and kisspeptin signaling pathway

The kisspeptin receptor (formerly known as GPR54, AXOR12, or hOT7T175) has a structure typical of Gq/11 proteins, and its activation triggers a signaling cascade via the phospholipase pathway [16]. Phospholipase C (PLC), activated by the Gαq subunit, catalyzes the conversion of phosphatidylinositol diphosphate (PIP₂) into two second messengers: diacylglycerol (DAG) and inositol triphosphate (IP₃) [17]. DAG activates protein kinase C (PKC), which in turn phosphorylates proteins in a downstream effector cascade. In addition, IP₃ binds to IP₃ receptors, many of which function as calcium channels (calmodulin), causing an increase in intracellular calcium levels and activation of various calcium-dependent processes in the cell [18].

This mechanism of the KP signaling cascade is primarily involved in triggering action potentials and regulating the secretion of gonadotropic hormones in the small cell nuclei of the hypothalamus [19].

Kisspeptins also initiate postsynaptic excitation of neurons in the dentate gyrus of the hippocampus in rats, indicating their significant role in learning and neurogenesis, according to studies by X. Liu et al. [20]. It is assumed that a similar mechanism underlies the vasoconstrictive properties of kisspeptins [16, 21], as well as their ability to increase the strength of heart contractions [22].

One of the mechanisms of deactivation of G protein-coupled receptors (GPRs) involves the coordinated actions of GPR kinases (GRKs) and β-arrestins-1 and -2. The interaction of the agonist with the *KISS1R* receptor triggers a process in which the heterotrimeric G protein breaks down into Gβγ and Gα-GTP subunits. For most GPRs, such as α-adrenergic receptors, the release of Gβγ subunits not only activates ion channels but also causes phosphorylation of the receptor by GPK2 kinase. Then, β-arrestins and elements of the ERK signaling pathway bind to the phosphorylated receptor via its second intracellular loop and C-terminal region, forming a complex that assembles in a clathrin-lined pit and transforms into an endosome [23]. It is important to note that for *KISS1R*, receptor desensitization also occurs in the presence of GRK2, but without phosphorylation [24]. Studies on the HEK 293 cell line (human embryonic kidney) have shown that most endosomes containing *KISS1R* return the



receptor back to the membrane rather than directing it for degradation [25].

Thus, the dynamic pool of KISS1R indicates that even temporary inactivation of these receptors does not prevent KP-10 from providing sustained stimulation of the cell. This assumption was confirmed in experiments on HEK 293 cells, where it was shown that exposure to kisspeptin-10 leads to prolonged activation of phospholipase C and protein kinase PLK enzymes, as well as an increase in intracellular calcium (Ca^{2+}) levels [24]. Moreover, H. Kroll et al. showed that kisspeptin is capable of mobilizing Ca^{2+} from intracellular depots not only during direct exposure to the peptide, but also after its removal from the culture medium [26, 27].

NATIVE AND SYNTHETIC KISSPEPTINS

Identification of key amino acids in the kisspeptin molecule that activate the receptor

Research in biochemistry and molecular biology has deepened our understanding of interaction between kisspeptins and their receptors. Determining the amino acid sequence that is necessary and enough to activate the kisspeptin receptor is one of the key aspects. In particular, it has been found that activation of the receptor by kisspeptin-10 depends on the C-terminal amino acid sequence -Phe6-Gly7-Leu8-Arg9-Phe10 [28].

A lot of data has been accumulated on synthetic agonists of the kisspeptin receptor (KISS1R), showing that certain modifications in the structure of peptides can significantly affect their ability to activate the receptor and cause biological effects, such as mobilization of intracellular calcium (Ca^{2+}). One such example is a pentapeptide with a 4-fluorinated benzene ring at Phe6, which has been shown to activate KISS1R and induce Ca^{2+} mobilization in CHO cells (Chinese hamster ovary epithelial cells), as demonstrated in studies [29, 30].

Studies have revealed that the amino acid residues Ser5 and Leu8 also play an important role in the activation of the KISS1R receptor [31]. It was found that changes in these positions can significantly affect the affinity of pentapeptides for the receptor, with the affinity of 5-amino acid peptides being significantly

lower than their 10-amino acid counterparts. These results highlight the importance of the precise structural configuration of peptides for their ability to interact with and activate the KISS1R receptor, which is important for the development of new therapeutic agents targeting this receptor pathway.

Experiments replacing individual amino acids in this sequence showed that replacing Phe6, Leu8, and Phe10 with alanine (Ala) and with dextrorotatory enantiomers results in a loss of affinity for the receptor. These findings indicate that the specific interaction of kisspeptin and the receptor greatly depends on steric factors, such as amino acid side chain orientation and overall peptide flexibility [32, 33].

Kp-13 appeared to have a helical structure with Asn7 to Phe13, and the receptor binding site is formed by Phe9, Arg12, and Phe13 [34].

A synthetic decapeptide with a dextrorotatory enantiomer Phe1 ([dY]1 NWNSFGLRF-NH₂) also showed lower affinity for the receptor *in vitro*, contrary to the previously mentioned study [33]. Differences between the two studies can be explained by various experimental methods. In the first case, a model of yeast transfected with the *KISS1R* gene and analysis of the activity of the *lacZ* reporter gene were used, which allows assessing the functional activity of the receptor under conditions close to natural ones. In the second case, a method of hybridization of a radioactively labeled peptide with membrane proteins of *KISS1R*-transformed CHO cells was used, which provides information about the direct interaction of the peptide with the receptor, but may not fully reflect its biological activity *in vivo*.

Despite differences in affinity, intraperitoneal administration of this analogue in a nanomolar dose to C57Bl/6 mice led to a significant increase in plasma testosterone levels. This indicates that when the affinity for the receptor is reduced *in vitro*, the analogue can be effective in stimulating the secretion of gonadotropic hormones *in vivo*, which emphasizes the importance of conducting studies on living organisms to evaluate the pharmacological activity of substances [32].

In order to evaluate the contribution of each side functional group of KP-10 to the agonistic activity of the molecule in relation to KISS1R and its interaction with the plasma membrane, a series of structural



analyses were performed, along with functional analysis, using alanine scanning (sequential replacement of each of the peptide amino acids with alanine). For this purpose, Gq/11-linked protein kinase C and a specific reporter system (c-fos-luc) were used in the functional analysis. Analogues with alanine substitutions at Tyr1, Trp3, or Ser5 showed similar activity to native kisspeptin-10, whereas alanine substitutions at Asn2, Asn4, Phe6, Gly7, Leu8, or Arg9 caused a clear decrease in agonist activity [31]. In particular, two analogues, F10A and the non-amidated form (NH₂-OH), did not exhibit GPR54 signaling activity. Similarly, it has been previously reported that the C-terminal quintet and amide group of kisspeptin-10 are important for specific binding to GPR54 and potent agonistic activity [35].

Thus, these results emphasize the importance of precise amino acid sequence and spatial configuration for the binding of kisspeptin to its receptor, which may be particularly important for the development of new drugs aimed at regulating reproductive function and other processes controlled by kisspeptins.

Comparison of kisspeptin-10 and kisspeptin-54

KP-10 and KP-54 are the two most commonly used forms of kisspeptin in research. It has been found that KP-10 undergoes rapid metabolism in mouse serum, with more than 50% of the peptide metabolized within the first minute after administration. This rapid breakdown of KP-10 may be associated with the presence of metabolically sensitive amino acid residues such as tyrosine (Tyr) and arginine (Arg) in its structure. These amino acids may make the peptide particularly vulnerable to the action of peptidases, enzymes that break down peptide bonds [36].

Native (natural) KP is metabolically unstable in blood and is hydrolyzed by various serum proteases and metalloproteinases, such as MMP-2 and MMP-9 [37]. The matrix metalloproteinase family is a group of structurally related zinc-containing endopeptidases that break down basement membranes and the extracellular matrix under physiological and pathological conditions [38, 39]. A number of studies have shown that the activity of type 2 or type 9 matrix metalloproteinases is suppressed by the protein kisspeptin. It is important to note that active MMPs can cleave the peptide bond between Gly 51-Leu 52 in the KP-54

protein sequence. As a result, three amino acids are cleaved from the N-terminus of the peptide, leading to the inactivation of KP-54, i.e., it can no longer perform its biological functions [40].

The half-life of KP-10 in humans is approximately 4 minutes [41]. This means that KP-10 is rapidly metabolized and eliminated, which may limit its therapeutic use without repeated or continuous administration.

Unlike KP-10, KP-54, consisting of 54 amino acids, is characterized by a longer half-life (approximately 28 minutes) [42]. The increased stability of KP-54 enhances its potential for clinical use, since it provides prolonged action with a single administration.

These differences in the pharmacokinetics of KP-10 and KP-54 may influence their selection in research and potential therapeutic applications, especially in the context of regulating reproductive function and other physiological processes involving kisspeptins. The pharmacokinetic properties of KP-54 make it more suitable for bolus administration than KP-10. A bolus of KP-54 causes a moderate increase in gonadotropin levels in healthy women in the follicular phase of the menstrual cycle, whereas a similar administration of KP-10 does not produce the same effect [41].

However, when KP-10 and KP-54 are administered continuously intravenously in equimolar doses to healthy men, they cause a similar increase in gonadotropin levels, indicating their effectiveness with this method of administration [43]. At the same time, gonadotropin levels (luteinizing hormone (LH) and follicle-stimulating hormone (FSH)) after administration of these kisspeptins are lower than after administration of gonadotropin-releasing hormone (GnRH), which may reflect differences in their mechanisms of action. Kisspeptins act at the level of the hypothalamus, stimulating the release of GnRH, while GnRH directly stimulates the pituitary gland to secrete gonadotropins.

Competitive binding experiments have shown that KP-54 and KP-10 have the same affinity for human and rat kisspeptin receptors, as confirmed by Ki (1.45–2.33 nM) and EC₅₀ (4.13–5.47 nM) values [6]. However, another study showed that KP-10 and KP-15 are five times more effective than KP-54, while KP-9 was less active [8]. The effectiveness of these kisspeptins was also proven by using the FLIPR (FLuorometric Imaging Plate Reader) method. This method allows



recording rapid changes in intracellular calcium (Ca^{2+}) concentration as an indicator of receptor activation. The study revealed a clear dose-dependent activity: at a concentration of KP 10^{-11} M, there was no significant release of Ca^{2+} , while in the range of 10^{-9} – 10^{-8} M, maximum activation of KISS1R was observed [36].

Short KP analogues have a potential therapeutic effect, however, like many other peptide hormones, they are subject to rapid enzymatic degradation, which limits their use, since high doses and/or frequent administration are required to achieve a therapeutic effect, which may be inconvenient for patients and may increase the risk of side effects.

Thus, the development of KP analogues that activate the kisspeptin receptor and are resistant to or inhibit the activity of matrix metalloproteinases may open up prospects for creating new antitumor drugs or replacing hormone therapy with already known hormones.

Modifications of kisspeptin that improve its stability in vivo

To improve the metabolic stability of KP *in vivo*, researchers can use various approaches, including:

- *modification of the amino acid sequence.* Changing certain amino acids in the peptide can make it less vulnerable to protein-cleaving enzymes.
- *introducing chemical modifications.* This includes incorporating phosphonic acids into the composition of KP or using synthetic amino acids that can increase its stability.
- *reducing the length of the amino acid sequence.* Shortening the amino acid sequence by removing sections that are easily cleaved by proteases (e.g., Tyr and Arg residues) can increase the peptide's resistance to metabolic breakdown in the blood and tissues.

Most research has focused on modifying the cleavage site.

It is known that peptides containing Arg are good substrates for trypsin-like proteases. Kisspeptin analogues in which Arg is replaced by neutral L-amino acids such as alanine (Ala), leucine (Leu), norleucine (Nle), and citrulline (Cit), which were supposed to prevent recognition and cleavage by trypsin, critically affected the activity of the molecule, reducing it by 21–110 times [44]. Thus, it is not advisable to replace Arg at position 53, as the basic amino acid at this position

appears to be necessary for the biological activity of the peptide.

Replacing an L-amino acid with the corresponding D-amino acid sometimes leads to an improvement in the biological activity of the peptide, as it changes the conformational properties of the peptide and increases its resistance to enzyme degradation [45], whereas no such effect has been observed with Arg.

Arg53 was modified in one study by methylating the guanidino group of arginine Arg (Me). During subsequent evaluation of its properties, it was found that the Nx-methylarginine analogue has stronger agonistic activity than KP-10 and is resistant to trypsin cleavage between positions 53 and 54 [46].

Phosphinic kisspeptin

Based on the primary structure of KP-10, two pentapeptides were developed and synthesized to improve the stability of the peptide [47]. The peptide bond between Gly-Leu was replaced with a phosphinic acid fragment $-\text{PO}_2-\text{CH}_2$. Synthetic peptides containing a phosphinic acid fragment substitution for the peptide bond are called KP-phosphinic peptides.

To verify the functional properties of the new synthetic peptides, their ability to bind and activate the kisspeptin receptor was evaluated. Human kidney cell culture HEK293 was selected as a model object for testing. This choice was due to the fact that HEK293 cells express the receptor for kisspeptins, which is important for embryonic kidney morphogenesis and glomerular development [48]. They also have low basal ERK1/2 phosphorylation activity (extracellularly regulated kinases 1 and 2, which are part of the MAPK cascade that plays an important role in transmitting signals from receptors on the cell surface to the nucleus).

The agonistic activity of KP phosphinic peptides against the kisspeptin receptor was evaluated by measuring the stimulation of ERK1/2 phosphorylation. The results showed that the phosphinic kisspeptin R-isomer (PKPR) is capable of binding with and activating the KISS1R receptor, as confirmed by a reliable calcium response at a concentration of 10 μM .

Phosphine peptides are known as potent and selective inhibitors of various proteases, such as MMP [49, 50], since their chemical structure mimics the intermediate transition state formed during peptide hydrolysis by proteases. It has been shown that PKPR



at a final concentration of 10 μM inhibited MMP-2 activity by 36%, while none of the synthesized phosphine peptides inhibited MMP-9 activity.

Clinical application of synthetic kisspeptins in treating reproductive disorders and oncology

Synthetic kisspeptins, which are peptides derived from the natural hormone kisspeptin, are used in clinical practice as potential therapeutic agents for treating various conditions associated with the reproductive and endocrine systems. The main areas of clinical application of kisspeptins are listed below.

1. Treatment of reproductive disorders

Hypogonadotropic hypogonadism: Kisspeptins can be used to stimulate GnRH release, which in turn activates the production of gonadotropins (LH and FSH) and helps normalize sex hormone levels. This may be particularly useful for treating patients with hypogonadotropic hypogonadism, including conditions such as Kallmann syndrome [13, 51].

2. Treatment of menstrual disorders and infertility

Induction of ovulation: Kisspeptins can be used to induce ovulation in women with ovulatory disorders, which may help in treating certain forms of infertility and may be used in *in vitro* fertilization (IVF) programs [52, 53].

Vitrification of ovarian tissue: Kisspeptins can be used as an agent to improve the quality of the cryopreservation environment by improving follicle maturation and increasing their viability after thawing [54].

Hyperprolactinemia: Administration of kisspeptin leads to an increase in LH levels in patients with both normal (in the case of hypothalamic amenorrhea) and elevated prolactin levels [55]. C.N. Jyasena et al. reported a tenfold increase in LH levels and a 2.5-fold increase in FSH levels after subcutaneous administration of kisspeptin-54 at a dose of 6.4 nmol/kg in women with amenorrhea against a background of hyperprolactinemia [56]. The number of studies confirming this relationship continues to grow. Thus, a positive effect was demonstrated after the administration of kisspeptin-54 to patients with hypothalamic amenorrhea, manifested at the onset of preovulatory LH levels [57].

3. Regulation of puberty

Delayed puberty: The administration of kisspeptins can stimulate the onset of puberty in children with delayed puberty [58].

Premature puberty: In theory, kisspeptin antagonists may be used to control or delay premature puberty, although this area requires further research [59].

4. Research in oncology

Tumor metastasis: Based on the role of the *KISS1* gene in suppressing tumor metastasis, kisspeptins may be investigated as potential agents for preventing the spread of cancer cells [4, 60].

Kisspeptins, particularly KP-10, are the subject of intensive clinical trials, reflecting their significant therapeutic potential. According to the clinicaltrials.gov registry in July 2025, 19 studies were completed to investigate the use of these peptides for treating such conditions as infertility, hypogonadotropic hypogonadism, and diabetes mellitus¹. The results confirm the potential of kisspeptins as therapeutic agents capable of modulating key physiological and pathological processes.

Currently, 12 other projects are actively ongoing, with a particular focus on the role of kisspeptins in carcinogenesis. These findings reflect the broadening of scientific interests and indicate their potential application in oncology. In-depth study of the modes of action and therapeutic potential of these peptides may open up new perspectives in treating various diseases, including those currently considered intractable.

To date, only two groups of researchers have taken steps in medical chemistry to develop kisspeptin receptor agonists with an improved pharmacological profile *in vivo* compared to native KP. The first group produced a series of decapeptide analogues of KP-10, in which one amino acid was replaced by an enantiomer or another amino acid, and the best analogue was tested *in vivo* for its ability to stimulate the gonadotropic axis [61].

The second group performed several modifications of the KP-10 sequence, resulting in several degradation-resistant analogues. The aim of this study was to reduce GnRH secretion by desensitizing KISS1R with an extremely long-acting agonist and, consequently, to reduce circulating gonadotropins and testosterone to castration levels, which is relevant for hormone-dependent cancer therapy [62, 63]. However, depending on the dosage regimen, an analogue of this type can also be used to stimulate the reproductive system.

¹ <https://clinicaltrials.gov/search?cond=kisspeptin>.



Thus, native kisspeptin is a natural ligand for the GPR54 (or KISS1R) receptor, which plays a key role in activating gonadotropin-releasing hormone (GnRH), which in turn stimulates gonadotropin secretion and regulates reproductive function. Native kisspeptin is effective in initiating this cascade, but its use is limited due to rapid degradation and low bioavailability. Synthetic kisspeptin analogues, including those with modifications to improve stability, have been developed to overcome these limitations. Modifications may include amino acid substitutions, the addition of protective groups that slow degradation, or changes to the molecular structure to improve receptor binding. These changes can significantly increase the half-life of the peptide in the blood, improve its ability to cross biological barriers, and enhance overall efficacy. Kisspeptin-based therapy may be productive in the treatment of malignant tumors, diseases associated with metabolic disorders, delayed puberty, and infertility. However, a short half-life limits the therapeutic potential of this molecule. Further research is needed to determine optimal dosages, administration regimens, and duration of therapy with kisspeptins, as well as to fully understand their potential side effects and interactions with other drugs.

ADDITIONAL INFORMATION

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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Review

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Stunning, malnutrition and microelement deficiency in Vietnam. Part 2. (Literature review of research in Vietnam)

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ABSTRACT. The second review devoted to the analysis of malnutrition studies in Vietnam systematizes the existing ideas about the prevalence, causes and methods of correction of stunting, malnutrition, vitamin and micronutrient deficiencies and anemia over a period of almost thirty years. The analysis of the cited sources showed that in 2003–2024, the prevalence of stunting among Vietnamese children aged 5–19 years decreased from 40–60% to 14–25%. The prevalence of malnutrition over the same period among children of the same age group decreased from 11–25% to 6–9%. Anemia for 2001–2024 also decreased from an average of 20–45% to 9–20% in school-age children, 30–35% in younger children, in newborns from 84–90% to 12–20%, in women of reproductive age from 40 to 20–25%. Regardless of the observation period, up to 60% of women of reproductive age and younger children and 11–40% of schoolchildren and adult men suffer from vitamin D deficiency. The prevalence of vitamin A deficiency in 2005–2024 was 6–14% in school-age children and 15–20% in newborns and women of reproductive age. Deficiency of microelements (zinc, selenium, magnesium, calcium) is registered in 50–60% of schoolchildren. Vitamin B₁₂ deficiency has been diagnosed in 3–15% of non-pregnant women and 8–12% of school-age children. The main factors of malnutrition, stunting, micronutrient and vitamin deficiencies are: anthropometric deficiency caused by malnutrition in parents, their low level of culture and education, inadequate breastfeeding, economic reasons for refusing to eat enough meat and vegetables, especially among residents of ethnic poor rural and mountainous regions, food shortages, as well as parasitic diseases and intestinal infections. Vitamin D deficiency is associated with traditional Vietnamese ideas about the physical attractiveness of a person with white skin.

Keywords: Vietnam, stunting, malnutrition, anemia, micronutrient deficiency

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РЕЗЮМЕ. Во втором обзоре, посвященном анализу исследований неполноценного питания во Вьетнаме, производится систематизация существующих в течение почти тридцатилетнего периода представлений о распространенности, причинах и методах коррекции задержки роста, недоедания, дефицита витаминов, микроэлементов и анемии. Анализ приведенных источников показал, что за 2003–2024 гг. у вьетнамских детей в возрасте 5–19 лет имеет место снижение распространенности низкорослости с 40–60% до 14–25%. Распространенность недоедания за этот же период у детей той же возрастной группы снизилась с 11–25% до 6–9%. Анемия за 2001–2024 гг. также уменьшилась со средних значений 20–45% до 9–20% у детей школьного возраста, 30–35% у младших детей, у новорожденных с 84–90% до 12–20%, у женщин репродуктивного возраста с 40 до 20–25%. Вне зависимости от периода наблюдения до 60% женщин репродуктивного возраста и младших детей и 11–40% школьников и взрослых мужчин страдают от дефицита витамина D. Распространенность дефицита витамина А за 2005–2024 гг. имела у 6–14% детей школьного возраста и у 15–20% новорожденных и женщин репродуктивного возраста. Дефицит микроэлементов (цинка, селена, магния, кальция) зарегистрирован у 50–60% школьников. Недостаточность витамина В₁₂ была диагностирована у 3–15% небеременных женщин и 8–12% детей школьного возраста. Основными факторами недоедания, низкорослости, дефицита микроэлементов и витаминов являются: антропометрический дефицит, вызванный недоеданием у родителей, низкий уровень их культуры и образования, неполноценное грудное вскармливание, экономические причины отказа от употребления достаточного количества мяса и овощей, особенно среди жителей этнических бедных сельских и горных регионов, дефицит продовольствия, а также паразитарные заболевания и кишечные инфекции. Недостаток витамина D связан с традиционными представлениями вьетнамцев о физической привлекательности человека с белой кожей.

Ключевые слова: Вьетнам, низкорослость, недоедание, анемия, дефицит микроэлементов

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INTRODUCTION

A previous review¹ reported that Vietnam, like many developing countries, is characterized by a double burden of malnutrition. This is a combination of high prevalence of undernutrition and obesity among people in the same area [1]. The main reasons for this situation in society are poverty in economically vulnerable regions and rapid urbanization in others, as well as changes in diet towards more calorie-dense, micronutrient-poor processed foods [2]. The second review discusses the prevalence and causes of stunting, underweight, and micronutrient deficiencies among the population of Vietnam, and presents the country's government strategy for preventing and treating these deficiencies.

AIM

The aim is to systematize existing knowledge accumulated over a period of almost thirty years regarding prevalence, causes, and methods of correction of stunting, malnutrition, vitamin and micronutrient deficiencies, and anemia in Vietnam.

ANALYSIS OF PREVALENCE AND CAUSES OF STUNTING IN VIETNAM

As shown in Table 1, from 1997 to 2003, more than 60% of children under the age of 10 were affected by stunting. Then, from 2005 to 2008, this figure decreased to an average of 38%. These data are consistent with those in the literature: L.M. Do et al. (2017) noted a decrease in the prevalence of stunting from 56.5% in 1990 to 30.7% in 2004. [3]. N.C. Khan et al. (2007), as a result of a repeat cross-sectional study from 1990 to 2005, also reported a significant decrease in the prevalence of stunting — from 45% in 1990 to 26.6% in 2004. [4]. In the following decade (2008–2017), there was a further decrease in the prevalence of stunting, which averaged 22% (ranging from 19% to 24%), with high values of this indicator

observed among rural children. The results presented in Table 1 also correspond to published data: according to the Vietnam National Nutrition Survey conducted by the National Institute of Nutrition in 2010, stunting in children aged 5–19 years amounted to 23.4%, and in 2015, it was 25%.

The data on the prevalence of short stature from 2018 to 2024, presented in Table 1, show some inconsistency. Most studies report that the indicator analyzed during this period does not exceed 14% and averages 8%, which is consistent with the results of the 2019–2020 Vietnam National Nutrition Survey conducted by the National Institute of Nutrition in children aged 5–19 (14.8%) and the data of S.K. Wake et al. (10 to 15%) [5]. However, other authors have not been able to confirm a decrease in the prevalence of stunting after 2019. For example, D.V. Chuc et al. (2019) reported stunting in 24% of rural children [6]. J. Gausman et al. (2019) reported that this indicator occurs in 20–25% of children under the age of 15, and decreases to 12% only in adolescents [7]. These results contradict the studies by J.A. Robinson et al. (2023), who found a prevalence of growth retardation in 60% of one-year-olds and 12-year-olds [8], and X. Tan et al. (2024), who found short stature in 26% of children aged 16 to 18 years [9]. However, T. Beal et al. (2019), T.T. Le et al. (2019), P.Y. Tan et al. (2024), and C. Mondon et al. (2024) report a prevalence of stunting in children under 5 years of age ranging from 20% to 44%, especially in ethnically diverse groups [2, 10–12]. It should also be noted that currently (2023–2024), rural children lag behind urban children in growth by a factor of 2–3 (Table 1). According to D.L. Minh et al. (2018), the incidence of growth retardation increased among urban girls (from 23.1% in 2013 to 42.3% in 2016) and rural boys (from 11.4% in 2013 to 18.0% in 2016) [13]. All of these discrepancies are most likely due to the heterogeneity of the study sample.

According to Table 1, the prevalence of short stature in children under one year of age did not change over time and averaged 12–14% (ranging from 3% to 23%) over the entire observation period (2005 to 2024). Some Vietnamese researchers associate growth retardation at 6 months of age with high levels of late gestational ferritin, a marker of oxidative stress, risk of intrauterine infection, and impaired uteroplacental blood flow

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Table 1

Prevalence of stunting in Vietnam according to various authors

Таблица 1

Распространенность низкорослости во Вьетнаме по данным различных авторов

Автор Author	Контингент Contingent	Возраст Age	Распространенность Prevalence
Hop et al., 1997 [24]	14-летнее лонгитюдное наблюдение, 212 детей (1981–1994 гг.) 14-year longitudinal follow-up of 212 children (1981–1994)	0–10 лет 0–10 years	♂ — 59,4% ♀ — 58,3%
Thang et al., 2003 [45]	Смешанная выборка, 4367 детей ¹ Mixed sample of 4367 children ¹	2–5 лет 2–5 years	58,8%
		6–11 лет 6–11 years	64,8%
Smuts et al., 2005 [46]	Смешанная выборка, 257 детей Mixed sample of 257 children	6–11 мес 6–11 months	8%
Watanabe et al., 2005 [47]	Смешанная выборка, 313 детей из провинции Тханьхоа Mixed sample of 313 children from Thanh Hoa province	6,5–8,5 лет 6.5–8.5 years	37,6%
Kulkarni et al., 2012 [48]	Смешанная выборка, 240 детей из сельской местности Mixed sample of 240 children from rural areas	5 мес — 2 года 5 months — 2 years	34,2%
Hien & Kam, 2008 [49]	Смешанная выборка, 650 детей из провинции Нгеан Mixed sample of 650 children from Nghe An province	0–5 лет 0–5 years	44,3%
Nhien et al., 2008 [25]	Смешанная выборка, 243 ребенка Mixed sample of 243 children	1–6 лет 1–6 years	36,2%
van Lierop et al., 2008 [50]	Смешанная выборка, 2613 детей из провинции Биньтхуан A mixed sample of 2613 children from Binh Thuan Province	6–10 лет 6–10 years	Городские — 17,3% City — 17.3% Сельские — 23,8% Rural — 23.8% Общая — 21,4% Total — 21.4%
Petrou & Kupek, 2010 [51]	Смешанная выборка, 2000 детей A mixed sample of 2000 children	6 мес — 1,5 года 6 month — 1.5 years	10–23,6%
Vaktskjold et al., 2010 [33]	237 детей из провинции Ханьхоа ² Mixed sample 237 children from Khanh Hoa province ²	Новорожденные Newborns	18%
Nakamori et al., 2010 [26]	Смешанная выборка, 188 детей из сельских районов Mixed sample of 188 children from rural areas	6 мес — 1,5 года 6 months — 1.5 years	23,4%
Le Nguyen et al., 2013 [52]	Смешанная выборка, 2872 ребенка Mixed sample of 2872 children	0,2–11,9 года 0.2–11.9 years	4% (<5 лет) (<5 years)
Ali et al., 2013 [53]	Смешанная выборка, 3075 детей Mixed sample of 3075 children	6 мес — 5 лет 6 months — 5 years	Легкая — 23,2% Mild — 23.2% Средняя — 27,8% Average — 27.8% Тяжелая — 25,6% Severe — 25.6%
Lundeen et al., 2014 [54]	Лонгитюдное исследование в течение от 1 до 8 лет Longitudinal study over 1 to 8 years	1 год 1 year	21%
		5 лет 5 years	24%
		8 лет 8 years	19,2%



Continuation of the Table 1 / Продолжение табл. 1

Автор Author	Контингент Contingent	Возраст Age	Распространенность Prevalence
Hanieh et al., 2015 [14]	Смешанная выборка, 1046 детей провинции Ханам Mixed sample of 1046 children from Hanam province	0–12 мес 0–12 months	6,4%
Dearden et al., 2017 [35]	Смешанная выборка, 1905 детей Mixed sample of 1905 children	1 год 1 year	19,7%
		5 лет 5 years	24,3%
		8 лет 8 years	19%
Georgiadis et al., 2017 [30]	Смешанная выборка, 2000 детей, лонгитюдное исследование Mixed sample of 2000 children longitudinal study	1 год 1 year	6%
		5 лет 5 years	4%
		8 лет 8 years	3%
Dat et al., 2018 [55]	Смешанная выборка, 6514 детей из провинции Биньдинь Mixed sample 6514 children from Binh Dinh province	6–10 лет 6–10 years	6,16%
Hoang et al., 2018 [56]	Смешанная выборка, 2334 детей из г. Хайфон Mixed sample of 2334 children from Hai Phong City	6–9 лет 6–9 years	5,1%,
Chuc et al., 2019 [6]	Смешанная выборка, 327 детей из Ким Донга, сельского округа провинции Хынгйен A mixed sample of 327 children from Kimdong, a rural district in Heungyeong Province	1–3 года 1–3 years	23,5%
Gausman et al., 2019 [7]	Смешанная выборка, 1833 ребенка Mixed sample of 1833 children	1 год 1 year	20,8%
		5 лет 5 years	25,4%
		8 лет 8 years	20,2%
		12 лет 12 years	19,4%
		15 лет 15 years	12,3%
Giao et al., 2019 [57]	Смешанная выборка, 768 детей из г. Хошимин Mixed sample of 768 children from Ho Chi Minh City	1–2 года 1–2 years	8,2%
Huynh et al., 2019 [22]	Смешанная выборка, 225 детей из больницы г. Хошимин Mixed sample of 225 children from Ho Chi Minh City Hospital.	6 мес — 5 лет 6 months — 5 years	22%
Beal et al., 2019 [10]	Смешанная выборка, 30 771 ребенок Mixed sample of 30,771 children	6 мес — 2 года 6 months — 2 years	17,5%
Beal et al., 2020 [58]	Смешанная выборка, 55 161 ребенок mixed sample of 55,161 children	2–5 лет 2–5 years	21,4%
Le et al., 2019 [11]	Смешанная выборка, 16 177 детей из горных районов, разные этнические группы Mixed sample of 16,177 children from mountainous areas, different ethnic groups	2–5 лет 1–5 years	29–43,9%
Mai et al., 2020 [1]	Смешанная выборка, 10 949 детей из г. Ханой Mixed sample of 10,949 children from Hanoi	6–18 лет 6–18 years	3,8%



Continuation of the Table 1 / Продолжение табл. 1

Автор Author	Контингент Contingent	Возраст Age	Распространенность Prevalence
Mai et al., 2020 [59]	Смешанная выборка, 10 949 детей 6–18 лет г. Хошимин Mixed sample of 10,949 children aged 6–18 Ho Chi Minh City	Младшие Juniors	2%
		Старшие Senior	8%
Quyen et al., 2020 [60]	240 детей до 2 лет округа Камкхе провинции Фу Тхо 240 children under 2 years old in Kam Khe district of Phu Tho province	6 мес 6 months	8,2%
		1 год 1 years	11,7%
		1,5 года 1.5 years	14,8%
		2 года 2 years	12,4%
Truong et al., 2022 [61]	Смешанная выборка, 1556 детей Mixed sample of 1556 children	средний возраст 12 лет average age 12 years	14,4%
Nguyen et al., 2023 [18]	340 детей из Национальной больницы акушерства и гинекологии г. Ханой 340 children from the National Hospital of Obstetrics and Gynecology in Hanoi	0–12 мес 0–12 months	14,1%
Robinson et al., 2023 [8]	Смешанная выборка, 1726 детей Mixed sample of 1726 children	1 год 1 years	58%
		8 лет 8 years	18,3%
		12 лет 12 years	56,8%
		15 лет 15 years	38,2%
Wake et al., 2023 [5]	Смешанная выборка, 9710 детей, лонгитюдное исследование Mixed sample of 9710 children, longitudinal study	В 2002 году In 2002	Умеренно — 15,1% Moderat — 15.1% Значительно — 5,7% Significant — 5.7%
		В 2006 году In 2006	Умеренно — 20,4% Moderat — 20.4% Значительно — 4,9% Significant — 4.9%
		В 2009 году In 2009	Умеренно — 16,9% Moderat — 16.9% Значительно — 3,2% Significant — 3.2%
		В 2013 году In 2013	Умеренно — 15,2% Moderat — 15.2% Значительно — 4,4% Significant — 4.4%
		В 2016 году In 2016	Умеренно — 10,2% Moderat — 10.2% Значительно — 2% Significant — 2%
Tan et al., 2024 [9]	Смешанная выборка, 2039 детей Mixed sample of 2039 children	6 мес — 2 года 6 months — 2 years	♂ — 14% ♀ — 7,7% Общее 10,9% Total 10.9%



Ending of the Table 1 / Окончание табл. 1

Автор Author	Контингент Contingent	Возраст Age	Распространенность Prevalence
Mondon et al., 2024 [2]	Смешанная выборка (обзор) Mixed sample (review)	5 лет 5 years	22,4%
Thuy Tran et al., 2024 [34]	Смешанная выборка, 4001 ребенок в возрасте от 0,5 до 11,9 лет из разных регионов Mixed sample of 4001 children aged 0.5 to 11.9 years from different regions	0,5–0,9 года 0.5–0.9 years	Городские — 3% City — 3% Сельские — 10,2% Rural — 10.2%
		1,0–3,9 года 1.0–3.9 years	Городские — 8,2% City — 8.2% Сельские 14,5% Rural 14.5%
		4,0–6,9 года 4.0–6.9 years	Городские 1,8% City — 1.8% сельские 11,3% Rural — 11.3%
		7,0–11,9 года 7.0–11.9 years	Городские — 3,5% City — 3.5% Сельские — 12,1% Rural — 12.1%
Tan et al., 2024 [62]	1471 девочка ³ 1471 girls ³	10–12 лет 10–12 years	12,4%
		13–15 лет 13–15 years	13,1%
		16–18 лет 16–18 years	26,8%
Tan, Chan et al., 2024 [12]	Смешанная выборка ⁴ Mixed sample ⁴	<5 лет <5 years	19,6%
		5–18 лет 5–18 years	3,7%

Note: ¹ages 2–11 years in 1992–1993 as part of the Vietnam Living Standards Measurement Surveys; ²born from one fetus between May and July 2005 in three main maternity hospitals; ³in 10–18 year old female participants in the 2020 Vietnam Nationally Representative Survey on General Nutrition; ⁴data on overall prevalence and prevalence stratified by sex and region were obtained from WHO/UNICEF/World Bank Group databases and national nutrition surveys (2018–2020).

Примечание: ¹возраст от 2 до 11 лет в 1992–1993 гг. в рамках Исследования уровня жизни населения Вьетнама; ²родившихся от одной матери в период с мая по июль 2005 года в трех основных родильных клиниках; ³участницы общенационального репрезентативного исследования Вьетнама по общему питанию 2020 года в возрасте 10–18 лет; ⁴данные об общей распространенности и распространенности, стратифицированной по полу и региону, были получены из баз данных ВОЗ/ЮНИСЕФ/Группы Всемирного банка и национальных обследований питания (2018–2020 гг.).

[14], as well as low levels of vitamin D [14]. According to other authors, the main cause of early onset of fetal and neonatal growth retardation is protein-energy malnutrition among pregnant women in rural areas of Vietnam [15], since other factors (heredity, environmental factors, etc.) can explain only 2–3% of intrauterine body length variation [16]. A mother's height of less than 145 cm and/or a body mass index (BMI) of <18.5 kg/m² in early pregnancy is a generally accepted criterion for high risk of giving birth to a baby with low weight in relation to gestational age [17], which is typical for Vietnam [10, 18]. M.F. Young et al. (2018) found these extremely low physical development indicators in 30% of women in Vietnam [19]. T. Beal et al.

(2019) reported that maternal height of 145–149 cm increases the risk of short stature in children by 49–62%, and less than 145 cm by 82% [10]. According to studies by M.F. Young et al. (2018) and P.H. Nguyen et al. (2021), short stature in children born to mothers with growth and weight deficits cannot be compensated for by the age of 2–7 years [19, 20].

Additional risk factors for low birth weight in Vietnam, according to the researchers, are maternal age over 35 years, serum albumin deficiency (an indicator of malnutrition), a history of anemia and premature birth [18], as well as birth weight <2500 g, maternal age <20 years, >2 children in the family [10, 21], child diarrhea, three or more children in the family [22], and



heavy physical work during pregnancy [23]. Some studies have shown that the growth of Vietnamese infants began to lag behind the Western control population from the age of 4–5 months due to inadequate introduction of complementary foods [24, 25].

Traditional beliefs can influence breastfeeding practices. Currently, the prevalence of breastfeeding among children aged 0 to 6 months is no more than 20% [26]. Some Vietnamese mothers perceive colostrum as a “dirty” product with no nutritional value, which leads to lower rates of initiation of breastfeeding [27]. Families, especially older members (mothers-in-law and grandmothers), friends, and neighbors play a significant role in shaping mothers' beliefs and practices regarding breastfeeding in infancy and adolescent nutrition [27, 28]. Physical and emotional support from husbands and families, as well as mothers' education, increase mothers' knowledge, beliefs, and confidence in following optimal breastfeeding practices [28]. In addition, the marketing of infant formula can negatively affect feeding practices in the first year of life by distorting information about dangers of breastfeeding [29]. It is therefore important to consider social and cultural traditions in future research aimed at improving child nutrition, especially in the context of limited resources and cultural diversity in Vietnam.

It is well known that social and economic factors such as the level of education, ethnic diversity, poverty, living in economically disadvantaged rural areas, and lack of access to health care facilities increase the risk of stunted growth [10, 30]. For example, children of mothers with no education or only primary education were 77% more likely to experience stunted growth than their peers born to mothers with higher education [10]. According to R.E. Black et al. (2013), about 15% of Vietnamese mothers do not have a sufficient level of education, which highlights the need to improve access to education for women [17]. It has been shown that parents with sufficient education are more responsive to specialists' recommendations regarding breastfeeding practices [31]. The close relationship between low maternal height and stunted growth in children in Vietnam indicates the importance of nutritional correction before and during pregnancy [17].

Tan et al. (2024) found that the well-being index was higher among adolescents who did not suffer from stunting [12], which is consistent with previous

studies that linked household well-being to the absence of stunting in children in developing countries, including Vietnam [32].

It has also been shown that the prevalence of short stature is higher among children from minority groups living in rural areas [10, 33, 34]. The risk of stunting among those surveyed living in the northeast of the country was twice as high as in the southeast, 72–83% higher than in the northwest, and 62–75% higher than in the central northern region and the Central Highlands [10]. This geographic pattern clearly reflects differences in social and economic status, the proportion of ethnic minorities, and access to food, health services, and clean water [35]. Such factors as small landholdings, the capacity of agricultural systems to provide sufficient food quality, and the level of government support pose a challenge to social and economic development in these regions [36]. Regional differences in risk factors for stunting suggest that regional policies should be adapted to address stunting, with priority given to ethnic minorities in the Central Highlands, as well as low birth weight children from low-educated families in the Southeast and mountain communities in the Northwest [10]. Living in a poor community was associated with an increased risk of stunting due to low social and economic status, both at the community level and at the level of individual households [37]. Studies show that children from ethnic minorities, poor families, predominantly rural and living in mountainous areas, do not have access to foods rich in nutrients such as meat, dairy products, eggs, fruits, and vegetables rich in vitamin A [12]. Social minority groups in Vietnam are much more likely to live in conditions of moderate or severe food insecurity and have less access to health services, improved sanitation, and water supplies available in urban areas [38]. For this reason, they have a higher prevalence of parasitic infections and diarrhea, leading to stunted growth in children under 5 years of age [39].

The US military launched a military campaign called “Operation Ranch Hand” during the Vietnam War to destroy the vegetation used by North Vietnamese troops for camouflage, during which herbicides were repeatedly sprayed in South Vietnam. It is estimated that between 1961 and 1971, ~77 million liters of herbicides, including 49.3 million liters of Agent Orange containing more than 360 kg of dioxin-contaminated defoliants, were sprayed several times over an area of



2.6 million acres [40]. In Vietnam, the number of people exposed or potentially exposed to Agent Orange was estimated at 4.8 million [40]. Studies from 1966 to 2002, summarized in reviews by J.E. Michalek et al. (1998) and A.D. Ngo et al. (2006), reported on the effects of Agent Orange and its dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin) used during the Vietnam War, on males and its relationship to short stature in their children [41, 42]. It is well known that organochlorine pesticides disrupt cell differentiation processes and endocrine regulation of growth and development [43], and their effects are transmitted across generations [44].

Thus, an analysis of growth retardation prevalence among children of all age groups over a period of more than 20 years showed a decrease in the percentage of short children in the Vietnamese population. Antenatal and infant growth retardation is usually the result of anthropometric deficiency in the mother caused by malnutrition and other factors related to her health, as well as her willingness to follow breastfeeding recommendations. Short stature in school-age and adolescent children is associated with social and economic factors: living in poor, rural mountainous areas and belonging to ethnic minorities.

ANALYSIS OF INCIDENCE AND CAUSES OF UNDERWEIGHT IN VIETNAM

The main trends in the incidence of underweight among children of different ages are shown in Table 2. The data show that until 2000, approximately 60–70% of school-age children were malnourished. Subsequently, the rate declined: from 2003 to 2013, malnutrition was recorded on average in 18% (from 11 to 25%) of children under the age of 12. However, the authors of two studies conducted in 2008 did not note a decrease in body mass deficiency during this period: N.N. Hien and S. Kam found malnutrition in 45–50% of younger children, while N. van Nhien et al. found it in older children (Table 2). From 2013 to 2017, there was a decrease in the percentage of malnourished children, and in 2018–2024, this indicator averaged 6% (3–9%) among children of this age. These facts are partially consistent with the literature data. A repeat cross-sectional study from 1992 to 2002 in children aged 2 to 17 years showed an increase in underweight from 32.1% to 33.5% [63].

There were differences between urban and rural children throughout the observation period. At the same time, according to studies conducted between 2008 and 2013, the prevalence of malnutrition among rural children was 6–15% higher than among their peers in large cities [13, 45, 50], while recent studies report that this difference is approximately 3–5% [1, 9, 34]. As noted, the causes of nutritional deficiencies, especially in rural areas, are: low economic status [2, 45, 49], insufficient access to food among rural residents [64, 65], inadequate diets in preschool institutions [66], a deficiency of macro- and micronutrients necessary for growth (protein, iron, zinc, vitamin D) [2, 9, 12], poor hygiene and contamination of drinking water sources [35], floods, droughts, or other natural disasters [2, 49], inadequate maternal nutrition [2], unsafe childbirth, and high infant morbidity rates [67]. It has been established that almost 60% of children aged 0.5–0.9 years and almost 90% of children aged 7–11.9 years did not follow the recommendations for energy, protein, calcium, iron, and vitamins A, C, and D intake [34]. The average measured total energy intake for Vietnamese residents was 2,196 kcal/day [28]. According to 2024 estimates, approximately 80% of children did not consume the amount of energy appropriate for their age [34]. Carbohydrates account for 65.6% of energy requirements, while fats and proteins account for 19.5% and 14.8%, respectively [28]. Approximately 55% of Vietnamese people have a low-fat diet, and the same percentage exceed the recommended level of carbohydrate consumption [28]. Only 5.2% of women of reproductive age achieved adequate consumption of n-3 and n-6 long-chain polyunsaturated fatty acids [28]. The main source of energy was rice and other starchy foods (62.6%), followed by meat and meat products (9.2%), and legumes/nuts/seeds and fruits (5% each). Animal products (meat, fish, eggs, and dairy products), excluding lard, accounted for 12.7% of total energy intake. Daily intake of protein, fat, and carbohydrates was 82 g, 49 g, and 356 g, respectively. Rice and other products were the main source of protein (30 g/day), followed by meat and meat products (17.7 g/day), as well as legumes, nuts, and seeds (7.9 g/day). The main sources of fat consumption in the diet were meat and meat products (14.0 g/day); oils, lard, and butter (8.6 g/day); and legumes, nuts, and seeds (6.1 g/day) [68]. Most of the



Table 2

Prevalence of malnutrition in Vietnam according to various authors

Таблица 2

Распространенность дефицита массы тела во Вьетнаме по данным различных авторов

Автор Author	Контингент Contingent	Возраст Age	Недостаток веса Underweight	Истощение Starvation
Giay & Khoi, 1994 [96]	Смешанная выборка взрослых Mixed sample of adults	26–40 лет 26–40 years	40%	
Thang et al., 2003 [45]	Смешанная выборка, 4367 детей 2–11 лет в 1992–1993 годах ¹ Mixed sample of 4367 children aged 2–11 years in 1992–1993 ¹	2–5 лет 2–5 years	57%	
		6–11 лет 6–11 years	71,4%	
Smuts et al., 2005 [46]	Смешанная выборка, 257 детей Mixed sample of 257 children	6–11 мес 6–11 month	12,7%	3%
Kulkarni et al., 2012 [48]	240 детей из сельской местности 240 children from rural areas	5 мес — 2 года 5 month — 2 years	15,8%	
Cuong et al., 2007 [97]	Смешанная выборка, 1488 взрослых из г. Хошимин Mixed sample of 1488 adults from Ho Chi Minh City	20–60 лет 20–60 years	20,4%	
Watanabe et al., 2005 [47]	Смешанная выборка, 313 детей из г. Тханьхоа Mixed sample of 313 children from Thanh Hoa city	6,5–8,5 лет 6.5–8.5 years	11,4%	
Tang et al., 2007 [98]	1504 подростка из г. Хошимин (равное количество ♂ и ♀) 1504 adolescents from Ho Chi Minh City (equal of ♂ and ♀)	Средний возраст 13,1 года Average age 13.1 years	13,1%	
Hien & Kam, 2008 [49]	Смешанная выборка, 650 детей из провинции Нгеан Mixed sample of 650 children from Nghe An province	0–5 лет 0–5 years	44,3%	11,9%
van Nhien et al., 2008 [25]	Смешанная выборка, 243 ребенка Mixed sample of 243 children	1–6 лет 1–6 years	50,2%	14,4%
van Lierop et al., 2008 [50]	Смешанная выборка, 2613 детей из провинции Биньтхуан Mixed sample of 2613 children from Binh Thuan province	6–10 лет 6–10 years	Городские — 16,7 % City — 16.7% Сельские — 22,6% Rural — 22.6% Общая — 20,4% Total — 20.4%	
Walls et al., 2009 [99]	Смешанная выборка, 4846 взрослых из г. Ханой Mixed sample of 4846 adults from Hanoi	25–74 года 25–74 years	13,3%	
Dieu et al., 2009 [100]	Повторное поперечное исследование 2002–2005 гг., 1162 ребенка Repeated cross-sectional study 2002–2005 1162 children	4–5 лет 4–5 years	7,5%	
Vaktskjold et al., 2010 [33]	237 детей из провинции Кханьхоа 237 children from Khanh Hoa province	Новорожденные Newborns	19,8%	
Dang et al., 2010 [101]	Исследование детей в возрасте 6–15 лет с 1992 по 2000 гг. в городских и сельских регионах с учетом их экономического положения ² A study of children aged 6–15 years from 1992 to 2000 in urban and rural areas, taking into account their economic status ²	Городские City	25,7%	
		Сельские Rural	34,8%	
		Бедные Poor	35,2%	
		Богатые Rich	23,5%	



Continuation of the Table 2 / Продолжение табл. 2

Автор Author	Контингент Contingent	Возраст Age	Недостаток веса Underweight	Истощение Starvation
Petrou & Kupek, 2010 [51]	Смешанная выборка, 2000 детей Mixed sample of 2000 children	6 мес — 1,5 года 6 month — 1.5 years	11,2–16,8%	7,6%
Nakamori et al., 2010 [26]	Смешанная выборка, 188 детей из сельских районов Mixed sample of 188 children from rural areas	6 мес — 1,5 года 6 month — 1.5 years	19,7%	5,3%
Nguyen, Eriksson et al., 2012 [102]	Смешанная выборка, 1495 детей из г. Ханой Mixed sample of 1495 children from Hanoi	Новорожденные Newborns	Городские ♂ — 2,3% City ♂ — 2.3% Сельские ♂ — 4,1% Rural ♂ — 4.1% Городские ♀ — 4,2% City ♀ — 4.2% Сельские ♀ — 4,9% Rural ♀ — 4.9%	
Ali et al., 2013 [53]	Смешанная выборка, 3075 детей Mixed sample of 3075 children	6 мес — 5 лет 6 month — 5 years	19,7%	5,7%
Ly et al., 2013 [103]	Смешанная выборка, 1713 взрослых жителей из г. Дананг ³ Mixed sample of 1713 adults from Da Nang City ³	≥35 лет ≥35 years	12,4%	
Nguyen et al., 2013 [68]	4983 небеременные женщины г. Тхай Нгуен 4983 non-pregnant women in Thai Nguyen City		31,71%	
Le Nguyen et al., 2013 [52]	Смешанная выборка, 2872 ребенка 0,2–11,9 лет ⁴ Mixed sample of 2872 children aged 0.2–11.9 years ⁴	<5 лет <5 years	8,6%	4,4%
		5–11,9 года 5–11.9 years	22,2%	
Dearden et al., 2017 [35]	Смешанная выборка, 1905 детей Mixed sample of 1905 children	1 год 1 year	3,8%	
		5 лет 5 year	3,9%	
		8 лет 8 year	11,7%	
Dat et al., 2018 [55]	Смешанная выборка, 6514 детей из провинции Биньдинь Mixed sample of 6514 children from Binh Dinh Province	6–10 лет 6–10 years	11,19%	10,79%
Hoang et al., 2018 [56]	Смешанная выборка, 2334 ребенка из г. Хайфон Mixed sample of 2334 children from Hai Phong City	6–9 лет 6–9 years	8%	5,3%
Minh et al., 2018 [13]	1955 детей в возрасте 5,5–6,5 года разного пола и возраста, городские и сельские 1955 children aged 5.5–6.5 years of different sexes and ages, urban and rural	В 2013 году In 2013	Общее — 9,2% Total — 9.2% Городские ♂ — 4,4% City ♂ — 4.4% Сельские ♂ — 17,5% Rural ♂ — 17.5% Городские ♀ — 3,4% City ♀ — 3.4% Сельские ♀ — 16,7% Rural ♀ — 16.7%	
		В 2014 году In 2014	Общее — 6,9% Total — 6.9% Городские ♂ — 12,3% City ♂ — 12.3% Сельские — 12,3% Rural ♂ — 12.3%	



Continuation of the Table 2 / Продолжение табл. 2

Автор Author	Контингент Contingent	Возраст Age	Недостаток веса Underweight	Истощение Starvation
			Городские ♀ — 2,5% City ♀ — 2.5% Сельские — 12,3% Rural ♀ — 12.3%	
		В 2016 году In 2016	Общее — 4,9% Total — 4.9% Городские ♂ — 3,0% City ♂ — 3.0% Сельские ♂ — 4,0% Rural ♂ — 4.0 % Городские ♀ — 3,6% City ♀ — 3.6% Сельские ♀ — 9,3% Rural ♀ — 9.3%	
Chuc et al., 2019 [6]	Смешанная выборка, 327 детей г. Хыньен Mixed sample of 327 children from Heungyeong City	1–3 года 1–3 year	7,6%	6,7%
Huynh et al., 2019 [22]	Смешанная выборка, 225 детей из больницы в г. Хошимин A mixed sample of 225 children from a hospital in Ho Chi Minh City	6 мес — 5 лет 6 month — 5 years	19%	10%
Pham et al., 2019 [104]	Смешанная выборка, 821 ребенок из г. Ханоя ⁵ Mixed sample of 821 children from Hanoi ⁵	11–12 лет 11–12 years	4,1%	
Mai et al., 2020 [59]	Смешанная выборка, 10 949 детей 6–18 лет из г. Хошимин Mixed sample of 10,949 children aged 6–18 Ho Chi Minh City	Младшие (город) Junior (city)	2–9%	
		Старшие (город) Senior (city)	6–18%	
		Сельские Rural	4,6%	
Quyen et al., 2020 [60]	240 детей до 2 лет из округа Камкхе провинции Фу Тхо 240 children under 2 years old from Kam Khe district, Phu Tho province	Новорожденные Newborns	15,6%	
		6 мес 6 month	3,9%	3%
		1 год 1 year	3,9%	1,3%
		1,5 года 1.5 years	1,3%	1%
		2 года 2 years	7,3%	2,3%
Truong et al., 2022 [61]	Смешанная выборка, 1556 детей Mixed sample of 1556 children	Средний возраст 12 лет Average age 12 years	5,4%	
Nguyen et al., 2023 [18]	Смешанная выборка, 340 детей ⁶ Mixed sample of 340 children ⁶	0–12 мес 0–12 month	12,4%	
Tan et al., 2024 [9]	1471 девочка 1471 girls	10–12 лет 10–12 years	9,4%	
		13–15 лет 13–15 years	5%	
		16–18 лет 16–18 years	2,7%	



Ending of the Table 2 / Окончание табл. 2

Автор Author	Контингент Contingent	Возраст Age	Недостаток веса Underweight	Истощение Starvation
Tan et al., 2024b [12]	Смешанная выборка, 2039 детей Mixed sample of 2039 children	6 мес — 2 лет 6 month — 2 years	♂ — 7,2% ♀ — 3,9% Общее — 5,6% Total — 5.6%	♂ — 3,6% ♀ — 3,2% Общее — 3,4% Total — 3.4%
Pham et al., 2024 [95]	108 мужчин и женщин из г. Хошимин ⁷ 108 men and women from Ho Chi Minh City ⁷	Пожилой возраст Old age	72,2%	
Mondon et al., 2024 [2]	Смешанная выборка детей Mixed sample of children	<5 лет <5 years	12,2%	5,2%
Thuy Tran et al., 2024 [34]	Смешанная выборка, 4001 ребенок в возрасте от 0,5 до 11,9 лет Mixed sample of 4001 children aged 0.5 to 11.9 years	0,5–0,9 лет 0.5–0.9 years	Городские — 5,1% City — 5.1% Сельские — 5,1% Rural — 5.1%	
		1,0–3,9 лет 1.0–3.9 years	Городские — 3,2% City — 3.2% Сельские — 2,8% Rural — 2.8%	
		4,0–6,9 лет 4.0–6.9 years	Городские — 6,6% City — 6.6% Сельские — 2,5% Rural — 2.5%	
		7,0–11,9 лет 7.0–11.9 years	Городские — 2,2% City — 2.2% Сельские — 7,5% Rural — 7.5%	

Notes: ¹Vietnam Living Standards Measurement Surveys; ² Vietnam Living Standard Survey (1992–1993), General Nutrition Survey (2000); ³ 900 households in 6 of 56 urban, rural and mixed urban-rural communities in Da Nang; ⁴the South East Asian Nutrition Surveys (SEANUTS); ⁵ National Hospital of Obstetrics and Gynecology in Hanoi; ⁶ Vietnam Nationally Representative Nutrition Survey 2020 (girls 10–18 years); ⁷hospital patients at the University Medical Center.

Примечания: ¹ Исследование уровня жизни населения Вьетнама; ² Исследование уровня жизни во Вьетнаме (1992–1993), Общее исследование состояния питания (2000); ³ 900 домохозяйств в 6 из 56 городских, сельских и смешанных городских-сельских общин в Дананге; ⁴ проект Обследования питания в Юго-Восточной Азии (SEANUTS); ⁵ Национальная больница акушерства и гинекологии в г. Ханой; ⁶ Общенациональное репрезентативное исследование Вьетнама по питанию 2020 г. (девочки 10–18 лет); ⁷ стационарные пациенты в Университетском медицинском центре.

protein requirement is met by low-calorie foods such as fish, crustaceans (shrimp, lobsters), mollusks (mussels), amphibians (frogs, snakes), and insects [69]. Data show a significant increase in the share of animal-based food consumption — from 12% in 1985 to 21% in 2010 [70]. Average per capita consumption of meat and poultry per day increased from 11 g in 1985 to 84 g in 2010. [70], oils and fats increased by 500% between 1985 and 2010, while vegetables decreased from 214 g per capita per day in 1985 to 190 g per capita per day in 2010 [70]. A large number of vegetables are a component of the diet mainly for residents of northern regions [71]. Children in Vietnam tend to have low consumption of nutrient-rich foods [72]. It was found that they consumed only 2.81 out of 7 groups of essential foods [72]. Only 39% of children consume dairy products [73], and

they prefer ultra-pasteurized (84%) and flavored (34%) milk, which has less nutritional value than natural milk [74]. Fast food consumption is also on the rise [70, 75, 76], while meat consumption is declining [77]. It is reported that whole grains, lean meat, fish, low-fat dairy products, and fresh vegetables and fruits are consumed more by groups with high social and economic status, while refined grains and added fats are associated with lower living standards [78].

A cross-sectional study conducted from October 2018 to April 2019 in the Three Tons District, Anxiang Province, found a high prevalence of low (21.4%) and moderate (70.4%) dietary diversity scores [38]. Dietary diversity was higher in households headed by men with sufficient education and income, as well as those exposed to media promoting proper nutrition and health,



with a high frequency of meals [38]. Low dietary diversity among Vietnamese people was directly correlated with sensory preferences regarding the appearance, smell, texture, and taste of food [79]. A monotonous diet is associated with slower linear growth in weight gain among Vietnamese children in their first two years of life [80].

Ethnic minorities living in mountainous areas are also at risk due to insufficient food supplies [2, 4, 45, 81] and a starchy, carbohydrate-rich diet [61, 82]. Truong et al. (2022) conducted studies in 2019–2020 and found that 14% of these children are underweight and 5.4% are severely malnourished [61]. A survey of children belonging to ethnic minorities found that 12.7–14% of participants regularly skipped breakfast and did not adhere to a healthy diet [61].

These regions experience food shortages for several months of the year between harvests [81], as well as seasonal fluctuations in the availability of protein and iron sources such as meat, fish, eggs, and seafood due to the inaccessibility of markets during the rainy season [83]. In addition, children in mountainous areas were less likely to consume foods such as fish, shrimp, crab, eel, snails, and mussels, as their mothers were simply unaware of the nutritional value and safe cooking methods for these seafood products [83].

Children from poor ethnic regions do not comply with hygiene requirements: washing their hands before eating and after using the toilet, undergoing deworming every 6 months [35, 61]. Poor sanitation is one of the main causes of high rates of stunted growth in mountainous areas [11, 84], as it can cause diarrhea and other digestive diseases [85]. Wastewater disposal measures [86] that improve sanitary conditions reduce the prevalence of diarrhea [87] and helminth infections [88] and decrease the prevalence of stunting [89].

Women from poor regions of Vietnam are more prone to mental illness, the prevalence of which is associated with stunted growth in their children [90].

A study by Upadhyay et al. (2021) reports a link between the use of solid fuels in economically disadvantaged households in Vietnam and the weight gain of children living there [91].

The prevalence of malnutrition among newborns and infants in their first year of life remained virtually unchanged during the observation period from 2005 to 2019, averaging 14% (ranging from 4% to 20%, Table 2). Only after 2020 did a downward trend to 4–7% emerge. Whether

this decline is a pattern rather than a random statistical fact will be determined by further observations, since the 2024 study notes that the nutrition of 80.1% of children did not meet their calculated energy requirements [34].

Factors associated with malnutrition, as well as growth deficiency, in newborns may include: the level of education of mothers [28, 34, 56], refusal to breast-feed [12, 26] and its insufficient quality [92], infectious diseases [12, 26], low birth weight [26], large families [93] father's insufficient involvement in family life [94], and single-parent families [12].

Based on the assessment of 13 indicators of optimal feeding practices for newborns and infants in their first year of life recommended by WHO/UNICEF, only 36.7% of children achieved the minimum dietary diversity, and only 29% achieved the minimally acceptable diet [62].

The highest percentage of malnutrition among the adult population was recorded in 1994 (40%) and in 2024 when observing individuals with pathologies. From 2006 to 2013, this indicator remained virtually unchanged, hovering between 13% and 20% (see Table 2). Thus, malnutrition is common among elderly patients and can lead to prolonged treatment, disability, and increased mortality among elderly residents of the country [84, 95]. Vietnam is one of the countries with a rapidly aging population. According to the 2019 statistical forecast, the number of elderly people is 11.41 million (11.86% of the total population), and it will double by 2038 [95].

Thus, more than 30 years of experience in monitoring the quantitative characteristics of malnutrition in Vietnam shows an approximately 5-fold decrease in malnourished school-age children. At the same time, the prevalence of underweight adults and newborns has remained virtually unchanged since 2008. The main causes of underweight are: traditionally high carbohydrate intake, low levels of education, lack of knowledge about healthy eating, increased consumption of fast food, poverty, especially in ethnic mountain areas, limited food security, environmental pollution, intestinal infections, and parasitic diseases.

ANALYSIS OF VITAMIN AND MICRONUTRIENT DEFICIENCY PREVALENCE AND ITS CAUSES IN VIETNAM

Table 3 shows that the prevalence of anemia among school-age children in 2001–2008 ranged from 20% to



Table 3

Prevalence of anemia, deficiency of trace elements and vitamins in Vietnam according to various authors

Таблица 3

Распространенность анемии, дефицита микроэлементов и витаминов во Вьетнаме по данным различных авторов

Автор Author	Контингент Contingent	Возраст Age	Анемия Anemia	Дефициты Deficits			
				Железо Iron	Витамин А Vitamin A	Витамин D Vitamin D	Микроэлементы Microelements
Hershman et al., 1983 [127]	161 взрослый из разных районов 161 adults from different areas	23–26 лет 23–26 years	–	–	–	–	Дефицит йода Iodine deficiency — 28–45%
Hall et al., 2001 [105]	588 детей ¹ 588 children ¹	7–11 лет 7–11 years	13%	–	–	–	–
Ta & Nguyen et al., 2003 [128]	284 девочки 284 girls	7–9 лет 7–9 years	–	–	7,1%	–	–
Smuts et al., 2005 [46]	257 детей 257 children	6–11 мес 6–11 month	89,9%	–	20,2%	–	Дефицит цинка — 22,5% Zinc deficiency — 22,5%
Nor & Berger, 2005 [129]	55 детей из г. Ханой 55 children from Hanoi	6 мес — 1 год 6 month — 1 year	84,9%	–	15,9%	–	Дефицит цинка — 22,5% Zinc deficiency — 22,5%
Aikawa et al., 2006 [130]	439 беременных женщин из провинции Нгеан 439 pregnant women from Nghe An province	–	43,2%	–	–	–	–
Nhien et al., 2008 [25]	243 ребенка из сельской местности 243 children from rural areas	1–6 лет 1–6 year	55,6%	–	11,3%	–	Дефицит цинка — 86,9% Zinc deficiency — 86,9% Дефицит селена — 62,3% Selenium deficiency — 62,3% Дефицит магния — 51,9% Magnesium deficiency — 51,9% Дефицит меди — 1,7% Copper deficiency — 1,7%
Khan et al., 2008 [131]	Сводная статистика у детей в возрасте до 5 лет Summary statistics for children under 5 years of age	–	20–40%	–	–	–	–
Pasricha et al., 2008 [117]	51 623 женщины, проживающие в округах Тран Йен и Йен Бинь 51,623 women living in Tran Yen and Yen Binh districts	–	37,53%	23,10%	–	–	–



Nhien N.V. et al., 2008 [25]	292 учащихся начальной школы из сельских районов 292 primary school students from rural areas	—	45%	11,3%	—	—	Дефицит цинка — 91,4% Zinc deficiency — 91,4% Дефицит селена — 75,6% Selenium deficiency — 75,6% Дефицит магния — 59,5% Magnesium deficiency — 59,5% Дефицит меди — 4,1% Copper deficiency — 4,1%
Van Nhien et al., 2009 [132]	245 девочек 245 girls	11–17 лет 11–17 years	20,4%	—	—	—	Дефицит цинка — 26,5% Zinc deficiency — 26,5% Дефицит селена — 15,9% Selenium deficiency — 15,9% Дефицит меди — 4,1% Copper deficiency — 4,1%
Vu et al., 2009 [133]	Небеременные женщины из г. Ханой Non-pregnant women from Hanoi	15–49 лет 15–49 years	19%	—	—	—	—
Casey et al., 2010 [108]	389 небеременных женщин из северных регионов 389 non-pregnant women from northern regions	Средний возраст 30 лет Average age 30 years	38%	19%	—	—	—
Phu et al., 2010 [112]		5 мес 5 month	40,8%	10,8%	—	—	—
Ho-Pham et al., 2011 [134]	205 мужчин и 432 женщины из г. Хошимин 205 men and 432 women from Ho Chi Minh City	18–87 лет 18–87 years	—	—	—	♂ — 20% ♀ — 46%	—
Fisher et al., 2011 [135]	413 беременных женщин провинции Ханам 413 pregnant women in Hanam province	—	—	—	—	—	Дефицит йода — 83% Iodine deficiency — 83%
Nguyen et al., 2012b [124]	269 женщин и 222 мужчины 269 women and 222 men	13–83 года 13–83 years	—	—	—	♂ — 16% ♀ — 20%	—
Hien et al., 2012 [136]	Беременные и небеременные женщины г. Ханой Pregnant and non-pregnant women from Hanoi	15–49 лет 15–49 years	—	—	—	48%	—



Continuation of the Table 3 / Продолжение табл. 3

Автор Author	Контингент Contingent	Возраст Age	Анемия Anemia	Дефициты Deficits			
				Железо Iron	Витамин А Vitamin A	Витамин D Vitamin D	Микроэлементы Microelements
Laillou et al., 2012a [125]	694 женщины 694 women	Репродуктивный возраст Reproductive age	–	38,4%	61,1%	–	Дефицит цинка — 91,8% Zinc deficiency — 91,8%
Laillou et al., 2013 [126]	532 ребенка 532 children	0–5 лет 0–5 years	–	–	–	21%	Дефицит кальция — 97% Calcium deficiency — 97%
Laillou et al., 2012b [137]	586 детей 586 children	6 мес — 6 лет 6 month–6 years	9,1%	12,9%	47,3%	–	Дефицит цинка — 51,9% Zinc deficiency — 51,9%
Laillou et al., 2014 [114]	1526 женщин 1526 women	Небеременные, репродуктивный возраст Non-pregnant, reproductive age	11%	13,7%	13,6%	–	Дефицит цинка — 67,2% Zinc deficiency — 67,2%
Le Nguyen et al., 2013 [52]	2872 ребенка 2872 children	0,2–11,9 года 0,2–11,9 years	38,65%	–	–	–	–
Le Nguyen et al., 2013 [52]	2872 ребенка 0,2–11,9 года (SEANUTS) 2872 children aged 0,2–11,9 years (SEANUTS)	2–4,9 года 2–4,9 years	18,25%	–	–	–	–
Siridamrongvattana et al., 2013 [107]	399 беременных женщин со сроком беременности <12 недель из Туа Тьен Хюэ 399 pregnant women <12 weeks of pregnancy from Thua Thien Hue	5–11 лет 5–11 years	12,47%	–	7,75%	–	–
Nguyen et al., 2013 [68]	254 беременные женщины из г. Хошимин 254 pregnant women from Ho Chi Minh City	–	–	–	–	–	Дефицит цинка — 25% Zinc deficiency — 25%
Tran et al., 2014 [138]	Беременные женщины на сроке от 12 до 20 недель Pregnant women from 12 to 20 weeks	–	Ранние сроки — 21,5% Поздние сроки — 24,4%	Ранние сроки — 4,1% Поздние сроки — 48,2%	–	–	–



Nguyen et al., 2014 [90]	4983 сельские женщины репродуктивного возраста 4983 rural women of reproductive age	-	Early pregnancy — 21.5% Late pregnancy — 24.4%	Early pregnancy — 4.1% Late pregnancy — 48.2%	-	-	-	-
Laillou A et al., 2014 [114]	1530 женщин репродуктивного возраста 1530 women of reproductive age	-	-	24,8%	27,1%	63,8%	Дефицит цинка Zinc deficiency — 15.6%	-
Poh et al., 2016 [139]	2016 детей 2016 children	2–15 лет 2–15 years	-	11,4%	При недостатке веса — 19% При ожирении — 7% Underweight — 19% / Obesity — 7%	11,1%	Дефицит цинка — 61,1% Zinc deficiency — 61.1%	-
Poh et al., 2016 [139]	SEANUTS, 2010/2011	-	-	-	-	Городские City ♂ — 9,3% ♀ — 14,7% Сельские Rural ♂ — 11,5% ♀ — 10,1%	-	-
Tuyen le D. et al., 2016 [121]	-	-	-	-	-	<5 лет — 58% <5 years — 58% 6–11 лет — 48,1% 6–11 years — 48.1%	-	-
Le Nguyen Bao et al., 2016 [109]	385 детей 385 children	6–11 лет 6–11 years	11,4%	5,6%	-	-	-	-
Nguyen et al., 2016 [15]	5011 беременных женщин 5011 pregnant women	-	1-й триместр — 18% 1st trimester — 18% 2-й триместр — 38% 2st trimester — 38% 3-й триместр — 34% 3st trimester — 34% Послеродовый 3-й мес — 38% Postpartum 3 months — 38%	13%	-	-	-	-



Ending of the Table 3 / Окончание табл. 3

Автор Author	Контингент Contingent	Возраст Age	Анемия Anemia	Дефициты Deficits			
				Железо Iron	Витамин А Vitamin A	Витамин D Vitamin D	Микроэлементы Microelements
			Послеродовая у детей — 42% Postpartum in children — 42%				
Chuc et al., 2019 [6]	327 детей г. Хыньен 327 children of Hung Yen city	1–3 года 1–3 years	33,3%	–	–	47,7%	–
Roos et al., 2019 [120]	Данные проекта SMILING ² SMILING project data ²	Разный возраст Different ages	17%	49%,	14,2%	–	–
Huynh et al., 2019 [22]	225 детей из больницы г. Хошимин 225 children from Ho Chi Minh City hospital	6 мес — 5 лет 6 months — 5 years	30,7%	–	–	–	–
Dat et al., 2019 [140]	1800 детей из провинции Биньдинь 1800 children from Binh Dinh province	8–10 лет 8–10 years	–	–	–	–	Дефицит йода Iodine deficiency Общее — 6,6% Total — 6.6% Городские — 5% City — 5% Сельские — 8% Rural — 8%
Hoang et al., 2019 [115]	893 ребенка сельских районов г. Хайфон 893 children in rural areas of Hai Phong	6–9 лет 6–9 years	Общая — 12,9% Total — 12.9% Микроцитарная — 7,9% Microcytic — 7.9% Нормоцитарная — 5,3% Normocytic — 5.3% Макроцитарная — 0% Macrocytic — 0%	–	–	–	–
Национальное исследование питания Вьетнама 2019–2020 гг. Vietnam National Nutrition Survey 2019–2020	Женщины Women	Трудоспособный возраст Working age	23,3%	–	–	–	Дефицит цинка — 42,6% Zinc deficiency — 42.6% Гиперкальциемия — 10,9% Hypercalcemia — 10.9%

Nguyen et al., 2021 [20]	Небеременные женщины Non-pregnant women	18–49 лет 18–49 years	–	–	–	–	–	Дефицит цинка — 85% Zinc deficiency — 85% Тяжелый дефицит цинка — 37% Severe zinc deficiency — 37%
Le Tuyen et al. 2022 [110]	Небеременные женщины Non-pregnant women	15–49 лет 15–49 years	25,5%	23,3%	–	–	–	–
Oktaria et al., 2022 [122]	Систематический обзор Systematic review	0–18 лет 0–18 years	–	–	–	0,9–96,4%	–	–
Tan & Chan et al., 2024 [12]	Обзор ³ Review ³	<5 лет <5 years	35%	20%	6%	39%	–	–
		5–18 лет 5–18 years	20%	13%	6%	40%	–	–
Tan et al., 2024b [9]	2039 детей 2039 children	6 мес — 2 года 6 month — 2 years	♂ — 32,4% ♀ — 29,9%	♂ — 40% ♀ — 28,8%	14,3%	–	–	Дефицит цинка — 56,7% Zinc deficiency — 56,7%
Thuy Tran et al., 2024 [34]	4001 ребенок из разных регионов 4001 children from different regions	0,5–11,9 года 0,5–11,9 years	12%	–	6,2%	31,1%	–	Дефицит цинка — 60% Zinc deficiency — 60%

Note: ¹here and below, a mixed sample is assumed unless otherwise stated; ²sustainable Micronutrient Interventions to Control Deficiencies and Improve Nutritional Status and General Health in Asia; ³overall prevalence data and prevalence stratified by sex and region were obtained from WHO/UNICEF/World Bank Group databases and national nutrition surveys (2018–2020).

Примечание: ¹здесь и далее подразумевается смешанная выборка, если не указано другое; ²устойчивые вмешательства для контроля дефицита и улучшения состояния питания и общего состояния здоровья в Азии; ³данные об общей распространенности и распространенности и распространенности, стратифицированной по полу и региону, были получены из баз данных ВОЗ/ЮНИСЕФ/Группы Всемирного банка и национальных обследований питания (2018–2020 г.).



45%. However, a single study conducted in 2001 failed to confirm these data [105]. Since 2010, there has been a decline in the number of anemic children, and in 2013–2024, this indicator averaged 13% (ranging from 9% to 20%). Anemia in younger children (aged 1 to 5 years) is an exception: according to some authors, its prevalence in 2019–2024 amounted to 30–35% [6, 12].

According to the data presented in Table 3, the prevalence of anemia in newborns also decreased from 84–90% in 2001–2005 to 38–40% in 2005–2019 and 12–20% in 2019–2024.

There was also a decrease in the number of anemic women of reproductive age and pregnant women (Table 3). While before 2013 this pathology was registered in more than 40% of those examined, in 2013–2022 anemia was diagnosed in 20–25% of women (according to some data, up to 35%).

These data are partially consistent with those found in the literature. A national study of nutritional risk factors in 1995 reported a high prevalence of anemia. Approximately 40–50% of young children and women were affected, but this figure fell after 2000 to 34% and 25%, respectively [106]. At the same time, iron deficiency anemia (IDA) was diagnosed in only 6%, while thalassemia accounted for 7.3% with a genetic predisposition of 26% of those examined, and 42.9% suffered from anemia for unknown reasons [107]. Adolescence is positively associated with anemia prevalence [9]. The low prevalence of IDA is confirmed by other authors. According to Casey et al. (2010), it occurs in 14% of non-pregnant women, Nguyen & Young et al. (2016) found it in 1.5% of pregnant women, and Le Nguyen Bao K. et al. (2016) observed it in 0.4% of children aged 6 to 11 years [20, 108, 109]. However, these data are inconsistent with the results of the 2010 National Nutrition Survey and the 2020 General Nutrition Survey in Vietnam. [110], which showed that about 37% of pregnant women suffer from IDA [111]. These results were reproduced by Phu et al. (2010), who showed that the prevalence of IDA remains quite high in children in their first year of life, at 21.7% [112].

At the same time, the prevalence of iron deficiency did not undergo significant fluctuations and corresponded to 11–13% (in some cases up to 40–50%) in school-age children, 10–12% in newborns, and 20–25% (in late stages 38–40%) in pregnant women and women of reproductive age.

The main causes of micronutrient and vitamin deficiencies are: the traditional preference of Vietnamese people for carbohydrate-starchy foods [28, 61, 82], modern trends towards an increase in the proportion of fast food in their diet [75, 76], and low consumption of fruits, vegetables, and meat due to their financial inaccessibility to residents of poor regions [38, 77]. According to studies by Bhutta et al. (2013), Hoang et al. (2019), Tan et al. (2024), poor nutritional status during pregnancy and in the neonatal period, maternal anemia, childhood stunting, and intestinal parasitic infections (giardiasis or ascariasis) were significant predictors of anemia in school-age children, while adequate consumption of iron-rich foods (meat, fruits, and vegetables) was a protective factor [9, 12]. Special studies have revealed low iron concentrations in the milk of women in Vietnam [113]. However, deficiencies in hemoglobin, ferritin, zinc, and vitamin A were not diagnosed in overweight individuals [114, 115]. Some studies have reported that iron deficiency is associated with malaria in ethnic minorities [116]. Anemia caused by parasites, especially hookworms, is a consequence of chronic blood loss [107]. Hookworm infection was the strongest factor associated with anemia, accounting for 22% of anemia cases [15]. Hookworm infections were significantly associated with hemoglobin levels [15]. In other studies, hookworm infection was not associated with anemia [117]. The most common parasites in Vietnam are *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), and hookworms (*Necator americanus* and *Ancylostoma duodenale*) [118]. Based on data from the Department of Parasitology and Malaria Control, Thua Thien Hue Health Service, the incidence of hookworm and malaria infection is quite low, with an average prevalence of 6.4% and <0.1%, respectively.

In 1985–1988, there was a high prevalence of clinical complications of vitamin A deficiency. Clinical assessment of vitamin A deficiency and xerophthalmia in more than 30,000 young children showed the presence of nyctalopia in 0.37% (WHO criterion no more than 1%), Bitot's spots in 0.16% (WHO criterion no more than 0.5%), corneal ulcers and keratomalacia in 0.07% (WHO criterion: no more than 0.01%), and corneal scarring in 0.12% (WHO criterion: no more than 0.05%) [119]. The prevalence of vitamin A deficiency remained relatively stable during the 2005–2024 observation period (Table 3): it was lowest among school-age child-



ren, ranging from 6 to 14% . Newborns and women of reproductive age accounted for 15–20% (in some cases up to 50% or more). At the same time, it is reported that vitamin A deficiency among children <5 years of age living in the Central Highlands and Northern Mountainous Regions is significantly higher than in other regions of the country (19–20%) [4, 120]. In the Red River Delta region, dark green leafy vegetables (average consumption 162 g/person per day) are the main source of plant carotenoids, while fruit consumption is quite low (52 g/person per day) [4].

The main risk factors for low serum retinol levels are a diet low in vitamin A sources (eggs, fruits, and vegetables), poor nutrition, and high levels of infections, particularly measles and diarrheal diseases [52], which are typical of low-income households [4].

Table 3 shows that, regardless of the observation period in Vietnam, up to 60% of women of reproductive age and young children (in some cases up to 90%) and 11–40% of schoolchildren and adult men suffer from vitamin D deficiency. Tuyen le D et al. (2016) found that the prevalence of vitamin D deficiency in adults increased from 7% (19% in pregnant women) in 2009 to 30% in 2012 and to 57% (36% in pregnant women) in 2013 among women living in Northern Vietnam. Deficiency of vitamin D varies greatly among different ethnic groups, they ranged from 0.9% to 96.4% in studies of Oktaria et al. (2022) and up to 58% in studies conducted by Stevens et al. (2022). Meanwhile, according to the authors [121], vitamin D deficiency is approximately twice less common in men than in women, which is consistent with the data presented in Table 3. Vitamin D deficiency increased from 22.8% in 2012 to 61.3% in 2015 among children under 6 months of age and from 66.7% in 2012 to 70.5% in 2014. among children aged 6 to 11 years in northern regions [121]. The SEANUTSII¹ (2021) [62] study showed a decrease in vitamin D deficiency compared to SEANUTS I (2011) [52]: 41.3% versus 52.7% for urban children and 23.3% versus 48.1% for rural children, respectively. The percentage of children suffering from vitamin D deficiency was higher in rural areas than in urban areas [71, 121]. Despite sufficient insolation (more than 100 sunny days per year²), vitamin D deficiency is a public health prob-

lem in Vietnam [122]. This phenomenon is explained by cultural traditions. Vietnamese people prefer wear closed clothing, use sun umbrellas, and have low outdoor activity, which limits their exposure to the sun [122], combined with low consumption of foods containing this vitamin, especially in children aged 6 months to 2 years [123]. Following rapid economic growth and increased cultural influence from Western countries, white skin has become part of the modern “concept of beauty,” which is particularly attractive to the younger generation of women [124]. In addition, the effectiveness of sun exposure may be reduced by air pollution, haze, and altitude [124]. It should be noted that significant predictors of vitamin D deficiency in women were urban residence and age under 30. The winter season was a significant predictor in men [124].

The analysis of micronutrient deficiencies is also presented in Table 3. Zinc deficiency varied depending on the gender, age, and place of residence. The highest values were found among rural children, pregnant women, and women of reproductive age (75–90%). Zinc deficiency among infants and older children did not exceed 60%. Selenium, magnesium, and calcium deficiency in all Vietnamese residents, regardless of sample type, ranged from 50 to 60%. Zinc and selenium deficiency was positively associated with stunted growth and malnutrition in school-age children and adolescents [9, 115, 125].

Vitamin B₁₂ deficiency was diagnosed in 3–15% of non-pregnant women [114, 126] and 8–12% of school-age children, regardless of gender and place of residence [125], due to insufficient consumption of meat and eggs [90]. However, there are no studies in Vietnam reporting the prevalence of macrocytic anemia [115].

A number of publications on iodine deficiency in Vietnam are limited. A 1983 study reported that iodine deficiency was found in 28–45% of adults, a 2011 study found it in 83% of pregnant women and women of reproductive age, and a 2019 study found it in 5–8% of schoolchildren (Table 3).

Therefore, 20 years of observations on anemia show a two- to threefold decrease in its prevalence among school-age children, pregnant women, and women of reproductive age. It is noteworthy that iron deficiency is not the leading cause of anemia among the Vietnamese population. Researchers attribute it to general protein-energy malnutrition and the spread of intestinal bleeding due to helminthic infestations. They

¹ Southeast Asian Nutrition Surveys

² <https://www.statista.com/statistics/1089265/vietnam-annual-sunshine-duration-in-by-city/>



also highlight nutritional causes in the spread of vitamin A and D deficiency due to the low consumption of eggs, meat, vegetables, and fruits among residents of poor rural areas. In addition, the cultural traditions of the Vietnamese people involve wearing closed clothing, which interferes with vitamin D synthesis in the skin. Subclinical deficiency of vitamin B₁₂, zinc, selenium, copper, and iodine should also be noted as a public health problem affecting the population.

KEY APPROACHES FOR PREVENTING AND TREATING DEFICIENCY DISEASES IN VIETNAM

Since the 1990s, starting with the First International Conference on Nutrition in 1992, Southeast Asian countries have adopted national nutrition strategies and action plans in order to eliminate the double burden of malnutrition (Food and Agriculture Organization of the United Nations, 1992; World Health Organization (2018a)). The WHO conducted Global Nutrition Policy Reviews in 2009–2010 and 2016–2017 (World Health Organization (2013), World Health Organization (2018a)). The Report on Food Security in ASEAN (Association of Southeast Asian Nations) prepared by European Union, UNICEF & World Health Organization in 2016, presented nutrition-related issues covered by national strategies in Southeast Asian countries. The national nutrition strategy sets out goals for improving nutrition and measures aimed at supporting vulnerable groups such as women and children belonging to ethnic minorities and living in poor areas [141], and implements a set of measures to reduce poverty, provide financial support to the population, provide credit, develop agriculture, and improve health care [2, 142]. Improving the nutritional status and diet of children has been a priority for the Vietnamese government since 2000. (National Nutrition Strategy for 2001–2010) [143]. Rapid economic development has helped to improve the nutritional status of the population, along with specific nutrition efforts by the Vietnamese government [141].

The National Nutrition Strategy for 2011–2020 with a vision for 2030¹ is a multi-sectoral policy document aimed at improving the quantity and quality of the

Vietnamese diet, reducing child undernutrition, and managing obesity and overweight. The vision for 2030 is to reduce child malnutrition below the level of public health significance and to increase the average height of adults. In addition, awareness of proper nutrition and behavioral change should be promoted among the general population to prevent nutrition-related chronic diseases, and food safety should be ensured.

The main objective of the current National Nutrition Strategy (Decision No. 02/QĐ-TTg 2022) for 2021–2030 and the Vision for the period up to 2045 is²: to promote proper nutrition for improving the nutritional status of each individual, location, region, and ethnic group, which will contribute to reduced morbidity and improved physical constitution, endurance, and intelligence among the Vietnamese people.

From 1993 to 2005, the Vietnamese government established a national target program to control iodine deficiency through widespread salt iodization. Iodized salt coverage increased to 95% of households, reducing the prevalence of goiter from 22% to 4% in children and increasing the average urinary iodine content from 32 µg/L to 130 µg/L in children aged 8 to 10 years [144]. Only 73.6% of respondents reported using iodized salt in any form in their households, while the target was 90% [135]. In recent years, Vietnam has achieved a significant reduction in child malnutrition thanks to positive effects of maternal and child health programs [145].

Clinically significant deficiencies are as follows: iron and zinc in children aged 6–8 months; iron only in children aged 9–11 months; vitamin B₂, calcium, iron, and folate in pregnant women; vitamins B₂, B₆, calcium, and folate in lactating women and adolescent girls; calcium and iron in non-pregnant women [146].

One measure to combat micronutrient deficiencies is to fortify foods with vitamins and micronutrients, for example, milk, vegetable oil, fish sauces, powdered flavorings, soy sauces, and wheat flour [137], infant formula and complementary foods [71], nutrient-dense complementary foods [147], rice³, instant noodles [148], cookies [149], and locally produced peanut bars

¹ <https://www.fao.org/faolex/results/details/en/c/LEX-FAOC142707/>

² <https://www.fao.org/faolex/results/details/en/c/LEX-FAOC213441/>

³ Nguyen T.T.L., 2024 Joseph M., Beesabathuni K., Matthias D. Enhancing the iron content of milled rice with path's ultra-rice® technology. http://www.path.org/publications/files/TS_ur_enh_iron_pos.pdf.



[150]. Fish sauce was identified as the most suitable food product for iron enrichment, as it is consumed by more than 80% of the population [144, 151] and has been effective in controlling iron deficiency anemia [144]. In 2011, the Vietnam Food Administration developed and issued national technical regulations on food enrichment, which further contributed to the creation of favorable conditions for food enrichment [144]. To support fish sauce fortification, the Global Alliance for Improved Nutrition awarded a grant to the National Institute of Nutrition for 2006–2009. This program achieved the production of fortified fish sauce in ten factories, reaching more than 575,000 people. The effectiveness of fish sauce fortification in improving iron status among women of reproductive age in Vietnam has led to a reduction in the prevalence of iron deficiency from 22.3% to 4.0% and anemia from 24.7% to 8.5% [151]. The average consumption of fish sauce in villages was 13–18 ml/person per day [151]. At this level of consumption, fortifying it with 7 mmol of iron/L would increase the added value of the sauce by 8%, which would amount to US\$0.11 per person per year [151].

In addition to fish sauce, vegetable oil, flavorings, and soy sauce are also target products for fortification, as they are consumed by 60–90% of the population [144]. Other measures include promoting breastfeeding, developing government-supported school feeding programs, and deworming to prevent iron deficiency [2, 71, 92, 106, 108].

Fortification of milk and biscuits with iron, zinc, iodine, and vitamin A, as well as increasing the calorie content of these products by an average of 300 kcal, contributed to accelerated growth and weight gain in children aged 1.5–2 years 5 months to 2 years after the start of consumption of fortified products [2, 149]. Enriching biscuits with several micronutrients is an effective strategy for improving the micronutrient status of Vietnamese schoolchildren and increases the effectiveness of deworming [148].

Adequate nutrition counseling programs that include information about the dangers of micronutrient deficiencies and social support, the creation of a flexible supplement intake scheme, and the involvement of community leaders in the promotion and marketing of dietary supplements and their free provision are positively perceived by the population [152].

Additional intake of dietary supplements containing micronutrients and vitamins is another way to correct deficiencies [2]. For example, prescribing supplements containing iron and folic acid before conception improved linear growth and fine motor skills in children aged 2 years [75]. Taking combined supplements containing zinc, iron, and vitamin A increased plasma retinol by 15% and reduced the prevalence of zinc deficiency by 17.3% [153]. The prescription of vitamin A capsules in 1988 reduced the prevalence of xerophthalmia [119]. Combined supplements containing zinc, iron, and folic acid, proteins, fats, and B vitamins, consumed by pregnant and lactating women, as well as children, in combination with dietary counseling, contributed to an increase in hemoglobin (decrease in the prevalence of anemia), ferritin, iron, zinc, plasma retinol, and urinary iodine in children and women [18, 60, 129, 138, 149]. Adding small amounts of locally produced fortified foods to the diets of Vietnamese women of reproductive age increased levels of iron, zinc, vitamin A, and vitamin B₁₂ [154].

Recent national dietary recommendations for pregnant women suggest adding fatty acids from the 16th week of pregnancy [155] to prevent congenital anomalies [156, 157]. Vietnam's National Nutrition Strategy for 2011–2020 does not mention encouraging the addition of fatty acids, as a result of which Vietnamese women may not be aware of their importance [155]. Congenital malformations that can be prevented with nutrient supplements remain one of the three leading causes of neonatal mortality in Vietnam [158]. The prevalence of anencephaly was estimated at 3.6 per 10,000 live births in Vietnam in 2010, which is higher than the corresponding figures in the United States (1.9–2.3 per 10,000 live births in 1995–2011) and Thailand (0.8 per 10,000 live births in 2001–2012) [158].

Vietnam has programs that focus on developing agriculture and small-scale animal husbandry. Both are seen as promising and culturally important ways to improve food security for the population [120]. Raising awareness about fruit and vegetable growing in home gardens and community gardens could reduce the financial burden of purchasing essential foods [159]. Promoting livestock farming at the household level could improve the supply of animal-based foods, which are rich sources of iron, zinc, and vitamin B₁₂. For example, the production of chicken liver (a source



of iron, zinc, and B vitamins), due to its affordability [146], will, according to some authors, help reduce malnutrition [146]. High consumption of dairy products has been associated with significantly higher concentrations of vitamin B₂, calcium, vitamins D and B₁, A, fat, protein, zinc, iodine, and bifidobacteria [160]. In order to implement agricultural development programs at the family level, the country has a Training and Implementation Center that promotes the improvement of veterinary services and animal breeding — Vuon Ao Chuong (“Garden Pond, Barnyard”) [159].

CONCLUSION

To sum up, it should be noted that over a period of almost 30 years, the Vietnamese government, thanks to the adoption of the National Nutrition Strategy, has managed to reduce the number of school-age children suffering from stunted growth and underweight by approximately 2–3 times. Measures introduced to enrich foods with vitamins and micronutrients have also led to a reduction in the number of children and adults suffering from anemia, iron deficiency, and vitamin A deficiency. However, vitamin D deficiency remains a public health problem, which is linked to traditional Vietnamese beliefs about the physical attractiveness of people with white skin. The main factors contributing to malnutrition, stunting, and micronutrient and

vitamin deficiencies are: anthropometric deficiencies caused by parental malnutrition, low levels of culture and education, inadequate breastfeeding, economic reasons for not eating enough meat and vegetables, especially among residents of poor rural and mountainous regions, food shortages, as well as parasitic diseases and intestinal infections.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Review

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The usage of the maximum inactive concentration as an analogue of the biological impact index for preventive health monitoring of chemical industry workers

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ABSTRACT. Introduction. In modern conditions of industrial production and enterprises, the problem of ensuring sanitary and hygienic requirements at the workplaces of employees who meet the established requirements of the legislation of the Russian Federation remains urgent. Problems associated with the possibility of contact with chemicals also remain relevant and have not lost their significance. When studying approaches to assessing the impact of industrial toxicants on the body of employees, the current and generally accepted method in the Russian Federation is the calculation method of “stay dose load”, which serves to substantiate the connection between the violation of the health status of workers and the accumulation of xenobiotics in the body. In order to prevent the accumulation of toxicants and organize measures to prevent occupational diseases, periodic medical and preventive examinations of employees are used, which are prescribed based on the results of a special assessment of working conditions, for workplaces with a recorded fact of exceeding the maximum permissible concentration in the air of the working area of harmful substances, typical for production. Today, in large enterprises where there is a chemical factor, the activities of industrial sanitary laboratories are aimed at registering the presence of chemicals in the air of the work area. Depending on the hazard class of the substance and the specifics of the technological process, the frequency of sampling and analysis is established. However, in order to implement measures aimed at preventing occupational diseases of workers, it is necessary to review approaches to the implementation of preventive monitoring. **The purpose** of the work is to prevent the negative effects of toxic substances on the body of workers and to take measures to organize a biomonitoring system at enterprises with potentially dangerous harmful substances. **Materials and methods.** A systematic analysis of modern literary sources and regulatory documentation in the field of occupational hygiene has been carried out. By the method of comparative analysis, domestic and foreign principles and practice of using approaches to assess the negative impact on the body of toxicant workers are compared. **Conclusions.** In order to organize preventive monitoring of the body condition of workers in contact with chemicals, it is necessary to supplement existing procedures for monitoring the working environment, such as special assessment of working conditions and production control, with a biomonitoring system to obtain a complete understanding of the impact of toxicants on the human body and subsequently assess the health risk.

Keywords: workplaces, maximum permissible concentration of air in the working area, maximum inactive concentration, chemical factor, biological exposure indices, selenium, occupational diseases

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Обзор

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Применение максимально недействующей концентрации как аналога индекса биологического воздействия для превентивного мониторинга здоровья работников химической отрасли

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РЕЗЮМЕ. Введение. В современных условиях деятельности промышленных производств и предприятий остается актуальной проблема обеспечения санитарно-гигиенических требований на рабочих местах сотрудников, отвечающих установленным нормам законодательства Российской Федерации. Проблемы, связанные с вероятностью контакта с химическими веществами, также остаются актуальными и не потеряли своей значимости. При изучении подходов по оценке влияния на организм работников промышленных токсикантов общепринятым в Российской Федерации является расчетный метод «стажевой дозовой нагрузки», который служит для обоснования связи нарушения состояния здоровья работников с накоплением в организме ксенобиотиков. В целях профилактики накоплений токсикантов и организации мер по предупреждению профессиональных заболеваний применяются периодические медико-профилактические обследования работников, которые назначаются на основе результатов проведенной специальной оценки условий труда, для рабочих мест с зафиксированным фактом превышения предельно допустимой концентрации в воздухе рабочей зоны вредных веществ, характерных для производства. В настоящее время на крупных предприятиях, где присутствует химический фактор, деятельность санитарных лабораторий направлена на фиксацию присутствия в воздухе рабочей зоны химических веществ. В зависимости от класса опасности вещества и особенностей технологического процесса по согласованию с местными органами Роспотребнадзора устанавливается периодичность отбора проб и их анализ. Однако для того, чтобы осуществлять мероприятия, направленные на предупреждение профессиональных заболеваний работников, необходимо пересмотреть подходы к осуществлению превентивного мониторинга. **Целью** работы является превентивное выявление негативного влияния на организм работников токсических веществ и принятие мер по организации системы биомониторинга на предприятиях, имеющих потенциально опасные вредные вещества. **Материалы и методы.** Проведен систематический анализ современных литературных источников, нормативной документации в области гигиены труда. Методом сравнительного анализа сопоставлены отечественные и зарубежные принципы и практика применения подходов по оценке негативного влияния токсикантов на организм работников. **Выводы.** Для организации превентивного контроля состояния организма работников, контактирующих с химическими веществами, необходимо дополнить существующие процедуры контроля состояния производственной среды, такие как специальная оценка условий труда и производственный контроль, системой биомониторинга для получения полного представления о воздействии токсикантов на организм человека и последующей оценки риска его здоровью.

Ключевые слова: рабочие места, предельно допустимая концентрация воздуха рабочей зоны, максимально недействующая концентрация, химический фактор, индекс биологического воздействия, селен, профзаболевания

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Publicly available online data provides indirect insight into the development of new technologies aimed at meeting Russia's economic needs in various fields, such as instrument engineering, the IT industry, and other related sectors.

The intensification of production technology development is also driven by the national needs for import substitution of raw materials, supplies, components, assemblies, machine parts, and equipment required for the aforementioned branches of the economy. Equipment and production technologies imported into Russia do not always comply with safety standards, including the equipment's potential to emit harmful substances into the environment.

Numerous workers are exposed to various pollutants at their workplaces, such as chemicals in the form of vapors, aerosols, and dust, which under certain conditions can adversely affect their health. In assessing the impact of toxicants entering the workplace air, it is customary to consider only the inhalation pathways of xenobiotic exposure. However, some of these substances can pose a greater health risk through dermal absorption. Therefore, an approach focused on comprehensive health screening and the implementation of biological monitoring for workers is warranted.

Inadequate control of occupational exposure to pollutants can lead to health deterioration. Some diseases caused by workplace hazardous substances (occupational diseases) may only manifest after a considerable latency period following initial exposure. Consequently, even the most effective treatment of an occupational disease will not prevent similar cases among other workers unless the sources of harmful exposure are eliminated. Hence, the risk of recurrence will remain persistently high. This underscores the critical importance of proactive strategies to protect the health of personnel handling hazardous substances, as well as others who may be indirectly affected by these work activities.

AIM

The aim of this study is to develop a framework for a preventive health biomonitoring system for chemi-

cal industry workers, utilizing the Maximum Inactive Concentration (MIC) as an analogue to the Biological Exposure Indices (BEI).

MATERIALS AND METHODS

Currently, two principal approaches are employed to control the levels of hazardous substances in workplace air: 1) the Special Assessment of Working Conditions (SAWC) procedure¹, and 2) the implementation of Production Control².

The existing SAWC procedure, as currently practiced, is designed to document the factors of the work environment and labor process at specific workplaces based essentially on the data provided by the employer commissioning the assessment. It is an open secret that violations of this procedure occur, leading to the recording of all environmental factor levels at or below established regulatory limits. Consequently, unscrupulous employers reduce costs by avoiding supplementary payments and compensations for hazardous working conditions, justifying this by claiming to protect workers' health through the provision of personal protective equipment. The inevitable result of such practices is an increase in occupational disease rates in the Russian Federation.

To monitor the content of harmful substances in workplace air, accredited measurement methods listed in the register of the accreditation body (the State Information Fund for Ensuring Measurement Uniformity, SIF UMI)³ are used. This can create a discrepancy, as the assessment of a chemical compound's concentration in the air may be impossible if no certified measurement method for it exists or has been developed.

¹ Federal Law No. 426-FZ of December 28, 2013 "On the Special Assessment of Working Conditions". Available at: https://www.consultant.ru/document/cons_doc_LAW_156555/ (accessed: June 8, 2024).

² Federal Law No. 52-FZ of March 30, 1999 "On the Sanitary and Epidemiological Welfare of the Population". Available at: https://www.consultant.ru/document/cons_doc_LAW_22481/ (accessed: June 8, 2024).

³ The official website of the "State Information Fund for Ensuring Measurement Uniformity — SIF UMI". Available at: <https://oei.by/mvvi/index> (accessed: June 8, 2024)..

Another significant factor compromising the objectivity of workplace assessment regarding chemical hazards is the sampling frequency and the specific time interval chosen for evaluation. According to SAWC guidelines, measurements must be conducted during the most intensive work shift, at peak equipment productivity and during the most demanding associated technological operations. In practice, this requirement is often disregarded during SAWC procedures, which calls into question the reliability of the obtained results.

RESULTS

Therefore, it can be concluded that the outcomes of a Special Assessment of Working Conditions (SAWC) may not accurately reflect the true state of the air quality in the workplace. Consequently, workers exposed to hazardous substances may be referred for mandatory periodic medical examinations. However, the preventive value of these examinations is compromised because the employer officially reports the absence of a chemical hazard.

A solution could be the implementation of a targeted biomonitoring program within the framework of enhanced occupational health examinations, using approaches analogous to Biological Exposure Indices (BEI). BEI represent guideline values for interpreting biomonitoring results. They serve as an additional tool for assessing the adverse effects of toxicants on workers and are instrumental in confirming exposure to a specific chemical agent¹.

A substantial array of methods for detecting xenobiotics in the human body exists and is employed in evidence-based medical practice in Russia. To establish regular monitoring of industrial toxicants and their metabolites in biological samples from workers, it is imperative to create a dedicated subsidiary structure within current specialized medical institutions for occupational disease research. This structure should have a sector-specific focus on existing enterprises and be based on biomonitoring. Concurrently, it is necessary to develop an algorithm for implementing approaches

that enable the early identification of health deviations in workers exposed to industrial toxicants.

The potential application of an analogue to BEI for organizing preventive health surveillance of workers with a confirmed chemical hazard at their workplaces is of significant interest.

One feasible approach to implementing xenobiotic detection can be illustrated using exposure to selenium compounds as an example.

Selenium finds wide application across numerous industrial sectors, both in the form of various salts and as a metallic powder. It is used in semiconductor technology, the production of high-quality alloys, pharmaceuticals, and the paint, varnish, and glass industries. The primary industrial uses of selenium are summarized in Figure 1.

Current estimates indicate a slight upward trend in global selenium consumption, including for the production of vitamin supplements and other goods [1].

The leading global selenium producers are Japan (accounting for 30–50% of world output), Canada (16–20%), Belgium (10–14%), and Germany (7%). Russia's share in global selenium production does not exceed 7% [2, 3].

At present, selenium production in the Russian Federation is carried out by three metallurgical companies: Norilsk Nickel (Norinickel), the Ural Mining and Metallurgical Company (UMMC), and the Kyshtym Copper Smelting Plant [4, 5].

Selenium production technologies remained virtually unchanged until the end of the 20th century. The dominant method was the roasting-selenide process, introduced in the 1970s at the Norilsk and Almalyk Mining and Metallurgical Combines and at the Ural Electrolytic Copper Plant (UralElectroMed). Copper

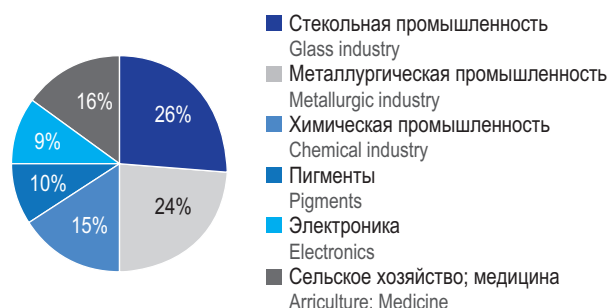


Fig. 1. Differentiation of industrial spheres of selenium application

Рис. 1. Распределение областей промышленности по применению селена

¹ International Labour Organization. Encyclopedia. Available at: <https://www.iloencyclopaedia.org/ru/part-iv-66769/biological-monitoring-65407> (accessed: June 16, 2024)..



slimes generated during the electrolytic refining of copper anodes were the primary industrial source of selenium.

Modern hydrometallurgical copper processing technologies implemented at metallurgical plants, primarily the SX-EW (Solvent Extraction — Electro-winning) process, developed in the 1980s by companies such as Phelps Dodge Corp. and Placer Dome, prevent the formation of anode slimes. These slimes were the traditional source of selenium [4, 6]. Current best practices focus on recovering selenium from various industrial process solutions and electrolytes.

During selenium extraction and refining, workplace air may become contaminated with various chemical compounds, including heavy metals and acid vapors. Workers directly involved in selenium production are at risk of exposure to these hazardous substances, which are released into the air from industrial equipment.

Consequently, a critical component of industrial hygiene is the systematic monitoring of airborne hazardous substances, coupled with health surveillance for employees exposed to such chemicals during their work^{1, 2}.

The time-weighted average Maximum Allowable Concentration (MAC) for selenium aerosol in workplace air is 2 mg/m³, classifying it as a hazard category 3 substance. For selenium dioxide aerosol, the maximum one-time exposure MAC is 0.3 mg/m³, while its time-weighted average MAC is 0.1 mg/m³, placing it in hazard category 1³.

A method for detecting selenium hexafluoride (SeF₆) in workplace air, along with the rationale for

setting its MAC (in vapor form) at 0.2 mg/m³ and assigning it to hazard category 1, was examined in a study by O.V. Gorbunova et al. [7].

Toxicological research on the effects of selenium hexafluoride in white outbred rats also led to the development of a bioindication method for selenium in biological matrices, specifically in the blood and urine of the test animals. This method was designed to establish an exposure test and for subsequent use in occupational hygiene control (biomonitoring) for workers handling the hazardous compound SeF₆ [7].

According to research data [8], selenium is excreted from the body via the kidneys. This finding supports the hypothesis that inhaled selenium hexafluoride, after undergoing metabolic transformations, is also partially eliminated in urine as various selenium compounds.

It is also established that selenium is present in the blood, including within the selenoenzyme glutathione peroxidase (GPx). GPx is detectable in virtually all human and animal tissues and biological fluids. Its enzymatic activity is significantly higher in blood plasma than in erythrocytes [9].

These considerations, together with the fact that blood and urine are the most accessible and convenient biological matrices for analysis, provided the rationale for selecting them as media for determining bodily selenium levels [10].

Dose- and time-response relationships for SeF₆ exposure — specifically, time-effect and concentration-effect curves — were established. Analysis of these relationships enabled an assessment of the compound's *general toxic effect* using a parameter S (following the methodology described in the source study [11]), which quantifies the deviation in the physiological state of exposed animals from that of controls. From this analysis, the *Maximum Inactive Concentration* (MIC) for chronic selenium hexafluoride exposure was determined to be 0.12 mg/m³. This MIC value can serve as a basis for designing biological monitoring programs for workers in hazardous occupations, as demonstrated for this specific xenobiotic in the doctoral thesis of O.V. Gorbunova [10].

In practice, however, such bioindication methods for harmful substances are employed merely as ancillary tools in evidence-based medical assessments and are not used to establish causality in occupational

¹ Federal Law No. 426-FZ of December 28, 2013 “On the Special Assessment of Working Conditions”. Available at: https://www.consultant.ru/document/cons_doc_LAW_156555/ (accessed: June 8, 2024).

² Federal Law No. 52-FZ of March 30, 1999 “On the Sanitary and Epidemiological Welfare of the Population”. Available at: https://www.consultant.ru/document/cons_doc_LAW_22481/ (accessed: June 8, 2024).

³ Decree of the Chief State Sanitary Physician of the Russian Federation No. 2 of January 28, 2021 “On the Approval of Sanitary Rules and Norms SanPiN 1.2.3685-21 ‘Hygienic Standards and Requirements for Ensuring the Safety and (or) Harmlessness of Environmental Factors for Humans’”. Available at: <https://docs.cntd.ru/document/573500115> (accessed: June 16, 2024).



disease or poisoning cases. Consequently, bioindication methods are not widely adopted for health screening of workers exposed to chemical hazards. This limited uptake can be attributed primarily to the need for a complex infrastructure involving specialized medical institutions tailored to specific industrial sectors. Furthermore, numerous logistical and regulatory barriers hinder the implementation of such monitoring systems.

An urgent need to revise current occupational health monitoring frameworks was identified. The key challenges for implementing biomonitoring in Russia include:

- the necessity to establish and accredit a large number of specialized sector-specific analytical laboratories for personnel health screening;
- the development and validation of modern biomonitoring methodologies;
- the study of toxicokinetics of hazardous substances upon entry into the human body;
- the rationale for selecting specific biological matrices for analysis.

Corresponding required measures at the enterprise level consist of:

- the timely identification of worker exposure to industrial toxicants and the implementation of protective measures;
- ensuring comprehensive coverage of at-risk worker groups for examination;
- the application of methods for ongoing control that enable the tracking of indicators related to the deposition of harmful substances in the body during work activities.

At the same time, global experience with Biological Exposure Indices (BEI) indicates their substantial benefits. This approach, focused on the early detection of health disorders among workers handling hazardous substances, delivers these benefits by reducing the incidence of occupational diseases related to chemical exposure [12]. However, studies demonstrate that occupational exposure limits enforced in the Russian Federation are more restrictive [3]. The numerical values of established Maximum Allowable Concentrations (MACs) for workplace air and Approximate Safe Exposure Levels (ASELs) differ significantly from corresponding BEI [8].

Nevertheless, BEI represent biomarkers that reflect the human body's response to chemicals ab-

sorbed via any route (e.g., inhalation, dermal, or oral). In some instances, BEI correspond to Threshold Limit Values (TLVs), defined as a "safe" level presumed not to induce adverse health effects. In others, they may represent the upper 95th percentile of biological response levels observed in a general population sample. Furthermore, certain BEI are non-numerical and provide only a qualitative indication of exposure. These indices are valuable for confirming that exposure to a specific chemical agent has occurred [13].

The data suggest that the Maximum Inactive Concentration (MIC), derived from continuous toxicological studies, could be considered an analogue to BEI [11]. An approach based on determining the MIC for different xenobiotics forms the basis for a risk-oriented concept in occupational risk assessment aimed at preventing toxicity-related occupational illnesses [14–16].

DISCUSSION

This study has evaluated the applicability of methodologies for assessing the adverse health effects of occupational chemical hazards. The conventional occupational hygiene assessment model in the Russian Federation relies on the Special Assessment of Working Conditions (SAWC) and routine production control. However, this model has been found inadequate for establishing an effective system for preventive health monitoring and the prophylaxis of occupational disease.

Consequently, instituting preventive health surveillance for workers in settings with chemical hazards requires the adoption of strategies centered on the early detection of substances to which exposure occurs during work activities.

This analysis has focused on two principal indicators for assessing chemical-related health impacts: the Biological Exposure Indices (BEI), standard in European and American practice, and the Maximum Inactive Concentration (MIC), utilized in the Russian context to validate exposure tests. The utilization of MIC holds potential for enabling the early identification of health impairments in workers and for mitigating the occupational risk associated with chemical factors.

A comparative analysis of the methodologies underpinning BEI and MIC application reveals that Bio-



logical Exposure Indices are not readily adaptable to the current occupational hygiene control framework in Russia. In contrast, the Maximum Inactive Concentration (MIC) presents a viable marker for the preventive diagnosis of health impairments in workers exposed to chemicals during the initial phases of exposure.

Therefore, within the current framework of the Russian Federation, a feasible preventive strategy can be implemented. This strategy involves assessing the adverse health effects on workers by applying analogues of the Biological Exposure Indices (BEI), such as the Maximum Inactive Concentration (MIC).

Currently, evaluating the adverse health effects of chemicals on workers relies on data from the Special Assessment of Working Conditions (SAWC), routine production control, occupational risk assessments, and periodic occupational health examinations.

This situation underscores the critical importance of ensuring safe and harmless working conditions for personnel at newly established or modernized workplaces. Furthermore, the current landscape of industrial advancement necessitates a revision of the methodologies used to assess workplace environmental factors that affect employee health.

CONCLUSIONS

Consequently, within the existing framework of legally mandated procedures, there is a clear need to

implement preventive health monitoring for workers at industrial facilities where chemical hazards are present. This analysis highlights the significant promise of further research focused on developing systematic preventive monitoring and health assessment strategies for workers exposed to diverse industrial toxicants [17–21].

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Review



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Translational animal models in the study of stress response regulation and complex mechanisms of glucocorticoid action

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ABSTRACT. In the literature analysis, the authors systematized information about the stress response, the main structures involved in this process, their gradual formation, development, and interrelationships that regulate the response to stress. The authors disclosed the role of using translational animal models in studying the development of the hypothalamic-pituitary-adrenal axis and the advantages and possible limitations that must be taken into account when planning a study to select a suitable model. The hypothalamic-pituitary-adrenal axis is a complex neuroendocrine system involved in responding to a stressor through multilevel interactions. The body needs to go through several critical periods of development in order to ensure the proper functioning of the hypothalamic-pituitary-adrenal axis and appropriate behavioral and physiological responses to stress in adulthood. The activity of the hypothalamic-pituitary-adrenal axis fluctuates throughout the day, these changes are ensured by the driver of the circadian rhythm and the suprachiasmatic nucleus, which regulate the circadian rhythms of glucocorticoids production. The heterodimeric *CLOCK/BMAL1* genes together with other transcription factors are responsible for circadian fluctuations in gene expression under the control of the biological clock system. The ultradian change in secretion depends on the pulsating release of corticosterone and adrenocorticotrophic hormone (ACTH) in response to different duration of stimulus and feedback signals within the hypothalamic-pituitary-adrenal axis. Glucocorticoids affect cells through genomic and non-genomic mechanisms. The non-genomic pathway is provided by interaction with plasma membrane-associated isoforms of glucocorticoid and mineralocorticoid receptors. The presence of these isoforms is confirmed in the limbic system, hippocampus, dendritic spines, pre- and postsynaptic membranes. The following models are considered as the most accessible and frequently used models for studying the stress response: zebrafish, rats and mice. The key points of the evolutionary development of these species, the features of the glucocorticoid axis formation (the structure of the glucocorticoid receptor, the course of the stress-hyporeactive period, the features of the main stress signaling molecule), which must be taken into account when choosing a model, as well as the possible limitations of each model, are formulated.

Keywords: hypothalamic-pituitary-adrenal axis, translational models, zebrafish, burrowing rodents, stress, glucocorticoids

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Обзор

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Трансляционные модели на животных в исследовании регуляции стрессового ответа и сложных механизмов действия глюкокортикоидов

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РЕЗЮМЕ. На основании анализа литературы в данном обзоре авторы систематизировали сведения о реакции организма на стресс, основных структурах, участвующих в этом процессе, их поэтапном формировании, развитии и взаимосвязях, обеспечивающих регуляцию ответа на стрессовое воздействие. Отдельно раскрыта роль применения трансляционных моделей животных в изучении развития гипоталамо-гипофизарно-надпочечниковой оси, преимущества и возможные ограничения, которые необходимо учитывать при планировании исследования для выбора подходящей модели. Гипоталамо-гипофизарно-надпочечниковая ось — сложная нейроэндокринная система, участвующая в реализации ответа на воздействие стрессора посредством многоуровневых взаимодействий. Организму необходимо пройти через несколько критических периодов развития, чтобы обеспечить правильное функционирование гипоталамо-гипофизарно-надпочечниковой оси и соответствующие поведенческие и физиологические реакции на стресс во взрослом возрасте. Активность гипоталамо-гипофизарно-надпочечниковой оси колеблется в течение суток, эти изменения обеспечиваются водителем циркадного ритма и супрахиазматическим ядром, регулирующим суточные ритмы выработки глюкокортикоидов. Гетеродимерные гены *CLOCK/BMAL1* в совокупности с другими транскрипционными факторами отвечают за циркадные колебания экспрессии генов под контролем системы биологических часов. Ультрадианное изменение секреции зависит от пульсирующего высвобождения кортикостерона и адренокортикотропного гормона в ответ на различное время действия стимула и сигналов обратной связи в пределах гипоталамо-гипофизарно-надпочечниковой оси. Глюкокортикоиды воздействуют на клетки посредством геномных и негеномных механизмов. Негеномный путь обеспечивается взаимодействием с ассоциированными с плазматической мембраной изоформами глюкокортикоидного и минералкортикоидного рецепторов. Наличие этих изоформ подтверждается в лимбической системе, гиппокампе, дендритных шипиках, пре- и постсинаптических мембранах. В качестве наиболее доступных и часто используемых моделей для изучения стрессового ответа подробно рассмотрены следующие модели: рыбы Данио-рерио, крысы и мыши. В данной статье впервые проведен сравнительный анализ рыб Данио-рерио, крыс и мышей с точки зрения трансляционной нейробиологии, рассмотрены аспекты формирования их гипоталамо-гипофизарно-надпочечниковой оси (строение глюкокортикоидного рецептора, течение стресс-гипореактивного периода, особенности основной стрессовой сигнальной молекулы), доступность, специфичность и другие характеристики, которые необходимо учитывать при выборе экспериментальной модели.

Ключевые слова: гипоталамо-гипофизарно-надпочечниковая ось, трансляционные модели, Данио-рерио, норные грызуны, стресс, глюкокортикоиды

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INTRODUCTION

Stress response is the body's reaction to internal or external factors. The hypothalamic-pituitary-adrenal (HPA) axis is a complex neuroendocrine system of direct and feedback pathways that function to maintain homeostasis. The HPA axis is involved in the response to stressors through multilevel interactions [1]. Abnormal development of the HPA axis in the long term can lead to changes in the synthesis of neuropeptides and neurotransmitters in the central nervous system, as well as the synthesis of glucocorticoid hormones in the periphery [2]. In combination, this can cause disorders of neuroendocrine, behavioral, autonomic, and metabolic functions in adulthood [2, 3].

The body must go through several critical developmental periods to ensure the proper functioning of the HPA axis and appropriate behavioral and physiological responses to stress in adulthood. The HPA axis begins to form already during intrauterine development and under the influence of hormones during puberty, it acquires sexual dimorphism [4, 5].

During stress, neurosecretory neurons in the paraventricular nucleus of the hypothalamus secrete corticotropin-releasing hormone (CRH). It induces secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland into the general circulatory system [6].

In the paraventricular nucleus of the hypothalamus, there are three types of functional neurons acting as central regulators of the stress response: magnocellular, parvocellular neurons, and long-projecting neurons [7].

Parvocellular neurons can regulate the secretion of releasing hormones into the hypothalamic-pituitary vascular network by connecting via their axons with the median eminence and thereby controlling the secretion of the corresponding hormones from the anterior pituitary gland. Magnocellular neurons project to the neurohypophysis, where they are involved in regulating the release of oxytocin and vasopressin into the systemic circulation. Long-projecting neurons send their axons to regions of the brainstem and spinal cord, where they control autonomic and somatosensory functions [8, 9].

The pituitary gland responds primarily to the release of releasing factors from the hypothalamus. The adenohypophysis accounts for 80% of the pituitary gland and contains special hormone-producing cells. These cells can synthesize and release hormones such as

growth hormone, thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, adrenocorticotrophic hormone, and prolactin [10, 11].

The adrenal glands are divided into the cortex and medulla. The medulla consists of chromaffin cells that secrete adrenaline and norepinephrine. Under the influence of the sympathetic nervous system, medulla cells actively respond to stress factors and release adrenaline and norepinephrine. As a result, changes in heart rate, blood pressure, and metabolism are observed [12]. Histologically, the adrenal cortex is divided into three zones. The outer zona glomerulosa produces aldosterone, which is involved in water and mineral balance. The intermediate zona fasciculata, the thickest region of the adrenal cortex, synthesizes glucocorticoids (GCs) (cortisol in humans and corticosterone in most rodents) and androgens [13, 14]. The zona reticularis also synthesizes adrenal androgens. It should be noted that dehydroepiandrosterone (DHEA) is the most abundant circulating adrenal androgen in adult humans, whereas its level is very low in adult rats and mice.

This work aims to study the structure and development of the HPA axis, as well as its role in regulating the stress response. Additionally, translational animal models used to study the development of the HPA axis and the impact of stress on the body are also presented and analyzed. Their advantages and disadvantages, which are important to consider when planning a study, are discussed.

ALTERATIONS IN THE ACTIVITY RHYTHM OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The levels of cortisol, the major glucocorticoid in humans, and its precursors vary in a predictable manner depending on time and on circadian, and ultradian patterns of secretion and excretion [15–17].

The daily activity rhythm of the HPA axis is determined by the circadian pacemaker, the suprachiasmatic nucleus. It plays an important role in regulating the activity of the paraventricular nucleus of the hypothalamus and the daily rhythms of GC production [18, 19]. Ultradian changes in GC secretion depend on the pulsatile release of corticosterone and ACTH, which occurs in response to variations in the timing of stimuli and feedback signals within the HPA axis. The ultradian rhythm, compared to the circadian rhythm, is not

under the influence of central regulation by the supra-chiasmatic nucleus but is probably generated by a direct pituitary-adrenal interaction during the constant administration of CRH [16, 20, 21]. Moreover, it has been shown that administration of high levels of corticotropin-releasing hormone leads to disruption of the ultradian pattern, with reduced fluctuations in corticosterone level. These repeatedly demonstrated the dose-dependent effect of CRH on patterns of GC secretion [17, 22, 23].

The HPA axis consists of stimulating signals and negative feedback mechanisms. Stress activates the HPA axis. CRH release in the hypothalamus triggers ACTH release from the pituitary and, ultimately, cortisol secretion from the adrenal glands. Cortisol, in addition to mediating subsequent physiological effects, also provides negative feedback to the HPA axis by suppressing the release of CRH and ACTH, thereby regulating its own activity [24, 25]. This negative feedback mechanism is essential for maintaining normal physiological levels

of circulating cortisol, enabling the body to preserve homeostasis in response to stress or illness.

GENES REGULATING CIRCADIAN RHYTHMS (THE CLOCK/BMAL1 HETERODIMER SYSTEM)

The CLOCK/BMAL1 heterodimers along with other transcription factors are responsible for circadian fluctuations in gene expression under the control of the biological clock system [17, 26, 27].

The biological clock system consists of a central clock and many peripherals. The central clock is located in the supra-chiasmatic nuclei of the hypothalamus, whereas peripheral clocks are ubiquitously expressed in all tissues [16, 28]. The central clock receives light/dark signals from the eyes via the retinohypothalamic tract and interacts with peripheral clocks, thereby synchronizing activity. Additionally, central and peripheral clocks use the same transcription factors, including CLOCK and BMAL1, to generate circadian rhythms of gene expression [29, 30].

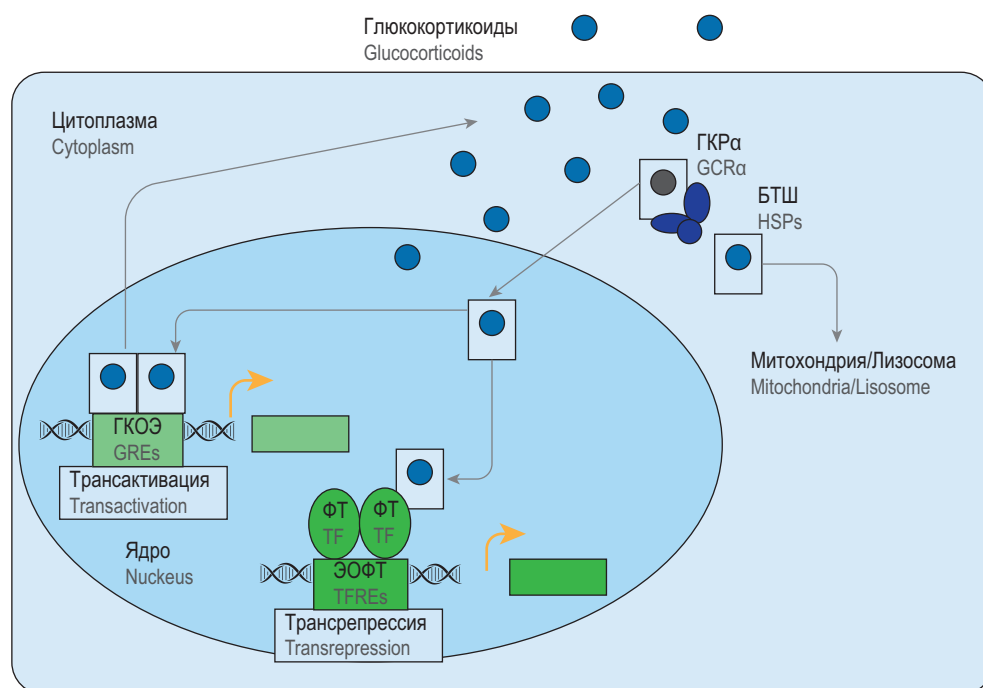


Fig. 1. Intracellular circulation of glucocorticoid receptors. The circulation of glucocorticoid receptors between the cytoplasm and the nucleus and the regulation of transcription of genes sensitive to glucocorticoids. Glucocorticoid receptors are further translocated into mitochondria or lysosomes [36]. HSPs — heat shock proteins; GCR α — glucocorticoid receptor α ; GREs — glucocorticoid response elements, TF — transcription factor, TFREs — transcription factor response elements (adapted from [162])

Рис. 1. Внутриклеточная циркуляция глюкокортикоидного рецептора. Циркуляция глюкокортикоидного рецептора между цитоплазмой и ядром и регуляция транскрипции генов, чувствительных к глюкокортикоидам. Глюкокортикоидный рецептор далее транслоцируется в митохондрии или лизосомы [36]. БТШ — белки теплового шока; ГКР α — глюкокортикоидный рецептор альфа; ГКОЭ — глюкокортикоид-отвечающие элементы; ФТ — фактор транскрипции; ЭОФТ/ФТОЭ — элементы ответа (отклика) факторов транскрипции / фактор транскрипции-отвечающие элементы (адаптировано из [162])



GCs are substances that can enter the cell membrane and influence cells by interacting with two types of cytoplasmic receptors: the low-affinity glucocorticoid receptor (GR) NR3C1 and the high-affinity mineralocorticoid receptor (MR) NR3C2 [30, 31]. MRs can also bind to another ligand, aldosterone. GR and MR are present in the cell cytoplasm as protein complexes with additional chaperone proteins. The released complexes translocate into the cell nucleus, where they suppress or enhance gene expression by binding to GC response elements in DNA [24, 32, 33].

Response elements are short DNA sequences within the promoter region of a gene that are capable of binding specific transcription factors and thereby regulating gene transcription. In case of stress, transcription activator proteins bind to response element and stimulate transcription (Fig. 1) [26, 34, 35].

GLUCOCORTICOID-DEPENDENT EPIGENETIC CHANGES

GCs are the main effectors of the stress response. The aberrant GC signaling is associated with an increased risk of mental and affective disorders, including schizophrenia, posttraumatic stress disorder, and depression [1, 31, 37].

Recent data report that chronic stress may modulate epigenetic “landscape” and influence function of genes, regulating stress response. Epigenetic modifications caused by stressors persist over time. This leads to increased susceptibility to various disorders associated with chronic or extreme stress [38, 39]. The interaction of GCs and receptors may exert epigenetic effects by altering the methylation state of specific regions of genomic DNA. This mode of GC action appears to underlie the long-term consequences of stress or contribute to cumulative stress [11, 40].

GCs have been shown to shape the epigenome through four main mechanisms, primarily involving glucocorticoid receptor signaling. Specifically, GCs can promote rapid demethylation of cytosine-guanine dinucleotides within glucocorticoid response elements [9, 41, 42].

In the study by H. Thomassin et al., it was found that GCs regulate DNA demethylation through a key enhancer of the rat liver-specific tyrosine aminotransferase (*Tat*) gene [42]. Demethylation is observed within 2-3 days after rapid (<1 h) chromatin remodeling and recruitment of the first transcription factor, HNF-3.

Since a stronger subsequent GC response is observed, demethylation appears to provide a memory of the initial stimulation. Demethylation occurs prenatally, at a stage when the *Tat* gene cannot yet be induced, allowing the enhancer to be prepared for subsequent stimulation by hypoglycemia at birth [42].

The mechanism underlying this effect involves GC-dependent activation of the transcription of enzymes that catalyze active demethylation (e.g., the TET family of 5-methylcytosine dioxygenases), as well as a reduction in the activity of DNA methyltransferases (e.g., DNA methyltransferase 1, DNMT1) [9, 43, 44]. Although GR signaling during stress is typically associated with demethylation processes, GR action has also been linked to methylation of a number of genes. GCs can induce histone modification, e.g., methylation and acetylation of histone proteins, either through direct binding of GR or through interaction with other transcription factors that recruit histone acetyltransferases [1, 45, 46]. GCs can regulate expression of several microRNAs, such as miR-218, miR-124, and miR-29a, possibly through interaction with GR, given that the genes encoding the altered microRNAs are enriched in sites predicted to be glucocorticoid response elements [38, 47].

GCs may affect chromatin remodeling through GR activation, altering the accessibility of genomic regions to transferases. Epigenetic changes induced by GCs can manifest both at specific loci and at the whole-genome level. For example, prenatal exposure to maternal depression was associated with lower levels of DNA demethylation throughout the genome [1, 48].

In the context of stress reactions or stress-associated disorders, the most widely studied epigenetic changes involve the genes *FKBP5* (506-binding protein 5), *NR3C1* (glucocorticoid receptor gene, nuclear receptor subfamily 3 group C member1), *BDNF* (brain-derived neurotrophic factor), *SLC6A4* (also known as *SERT*; 5-HTT; 5-HTTLPR, encodes a sodium-dependent transmembrane transporter, a reuptake protein of the neurotransmitter serotonin) and *OXTR* (Oxytocin receptor, the gene encoding the oxytocin receptor) [49].

MECHANISMS OF GLUCOCORTICOID INFLUENCE AT THE GENOMIC LEVEL

Phase 1 — basal phase. Under non-stress conditions, intracellular MRs are occupied by low basal



concentrations of GCs due to the high binding affinity. Under stress conditions, GC secretion promotes an increase in GC binding to receptors having lower affinity. Thus, an increase in GCs concentration leads to a rapid increase in the number of active receptors. As a result, the threshold for triggering the stress response is regulated by GC binding to MRs, while short-term activation of GRs ensures rapid adaptability to respond to acute changes in GC levels [50].

Phase 2 — initial phase. When a stress response that threatens homeostasis is triggered, CRH secreted by the hypothalamus stimulates secretion of GC from the adrenal cortex. To rapidly enhance attention and recognize threats, membrane-bound mineralocorticoid receptors (mMRs) undergo a series of non-genomic changes.

mMR-induced neuronal excitability ensures the retrieval of memory regarding previous stress-coping strategies, while in the amygdala region, the fight-or-flight response is activated.

The choice of strategy for coping with stress is determined specifically by limbic MR activation: minor stressful stimuli trigger a “thinking” strategy rather than an “action” strategy, the latter of which enhances amygdala activity [38, 51].

Phase 3 — terminal phase. As GC levels rise, activation of low-affinity GRs suppresses the stress response through negative feedback.

Transcription-independent and transcription-dependent GR mechanisms sequentially mediate negative feedback:

- 1) fast, at the hypothalamic level through inhibition of chrysin (CRH) and the pituitary level through inhibition of ACTH (<10 min);
- 2) intermediate, due to the effect on the paraventricular nucleus (30 min - 2 hours);
- 3) slow and prolonged, which is achieved through the suppression of proopiomelanocortin expression (>3 hours).

At the same time, due to transcription regulation mechanisms, GR promotes the mobilization of the body's energy resources to return to the basal state.

Phase 4 — priming. GR mediate the retention of stress-related memory in the hippocampus and the strategies used to overcome stress. In the case of repeated stressful impacts, MR activation contributes to the consolidation of this experience in memory [52].

During the priming stage, GRs induce activation of the NF- κ B/NLRP3 inflammasome pathway, which can potentiate the neuroinflammatory response to a subsequent pro-inflammatory stimulus. This mechanism has been proposed to explain the paradoxical pro-inflammatory effects of GCs, which are traditionally regarded as anti-inflammatory agents [38].

It was demonstrated that an immobilization stress-induced increase in serum GC concentration does not change the density of IL-1 receptors in the hippocampus of mice at rest and after peripheral injection of lipopolysaccharides [34, 53]. Importantly, IL-1 and IL-6 also did not affect the expression of glucocorticoid and mineralocorticoid receptors. In contrast, hippocampal GR expression was significantly reduced following TNF α injection. Thus, IL-1 receptor levels in the hippocampus are relatively resistant to modulation by circulating GCs, whereas TNF α significantly influences the HPA axis activity during immune or inflammatory processes [30, 54, 55].

Moreover, GCs show non-genomic effects on cell functions independent of gene transcription and protein synthesis through interaction with plasma membrane-associated isoforms of GRs and MRs. The presence of such isoforms of GRs and MRs was confirmed in the limbic system, particularly in the hippocampus, dendritic spines, pre- and postsynaptic membranes. Such localization of GR and MR isoforms suggests that GCs have a direct effect on synaptic transmission and dendritic spines formation [50, 56, 57].

Thus, under physiological conditions, GCs are the main stress regulators that promote adaptation of the body. However, repeated or severe stress can disrupt the glucocorticoid-regulated response mechanism, leading to a loss of the body's ability to withstand internal and external stressors, thereby increasing vulnerability to disease and aggravating existing pathologies.

PHYSIOLOGY AND EMBRYONIC DEVELOPMENT OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS IN DIFFERENT ORGANISMS

Features of the hypothalamic-pituitary-adrenal axis in zebrafish

It is known that the evolution of vertebrates has been greatly influenced by whole-genome duplication.



Moreover, the first two duplications occurred during period of vertebrate evolution approximately 560 and 530 million years ago, and the third occurred specifically in ancient fish about 320–350 million years ago [58]. The third whole-genome duplication resulted in the emergence of number gene duplicates. Currently, these genes are observed exclusively in teleosts. This means that the genome of these fish contains two genes encoding the GR [59]. These isoforms are called GR1 and GR2. Both GRs are functional receptors. However, it is assumed that they are activated at different cortisol concentrations *in vivo* [58, 60].

After whole-genome duplication, most duplicate genes are lost due to nonfunctional mutations lead to pseudogenes formation. However, in some cases, duplicated genes are retained and undergo subfunctionalization, in which both genes retain parts of the original gene function, or neofunctionalization, in which one copy acquires a new function [61]. Duplicate genes may also be retained to provide genetic stability [62].

However, unlike most teleosts, zebrafish possess only a single copy of the GR gene. In this species, two splice variants of the gene, GR α and GR β , were identified [61]. GR α binds cortisol with high affinity and is transcriptionally active, whereas GR β does not bind cortisol and lacks the same transactivation properties. GR β has also been shown to inhibit the activity of zebrafish GR α , a feature that distinguishes them from other teleosts and makes this species an excellent model for studying GCs in the regulation of the stress response [63].

Zebrafish are the only known teleosts with a single GR gene. This suggests that GR signaling is critical for HPA axis activation after hatching. Genomic cortisol signaling may play a key role in the organization of metabolism and energy redistribution at the critical stage of first feeding and growth of zebrafish, as well as in overcoming stress. This assumption is supported by the higher tissue metabolic capacity and enhanced glucose metabolism in response to genomic cortisol signaling in teleosts, as well as by the lack of cortisol stress response before hatching [64].

In fish, cortisol secretion is regulated by stress axis, as in mammals (Fig. 2). However, there are anatomical differences in fish and mammals. The adrenal gland in mammals is homologous to the interrenal gland in fish, a structure embedded in the anterior part

of the kidney. The hypothalamus and pituitary gland during the larval stages are formed along an anterior/posterior axis, in contrast to similar structures in mammals, which are formed along a dorsal/ventral axis.

Additionally, the pituitary gland of zebrafish is located closer to the hypothalamus than the pituitary gland of mammals.

When stress occurs, the hypothalamus initiates the stress response by secreting CRH. In zebrafish embryos, using whole-mount *in situ* hybridization, CRH-positive cells were first detected 24 h post-fertilization in the preoptic area (zebrafish hatch at approximately 48 hours post-fertilization). There is limited evidence regarding an increase in CRH mRNA content between 1 and 5 days post-fertilization using reverse transcription polymerase chain reaction (PCR), suggesting the development of stress perception mechanisms leading to HPA axis activation during this period in zebrafish [65].

However, it remains to be determined whether this possible regulation of CRH transcripts reflects increased sensitivity to stressor exposure during this developmental period.

In fish, CRH-secreting hypothalamic neurons terminate in the anterior pituitary gland, specifically in the corticotropic and melanotropic cell regions. In response to CRH stimulation, corticotrophs release ACTH into the bloodstream (Fig. 2).

ACTH is formed by post-translational cleavage of the protein encoded by the proopiomelanocortin (POMC) gene [66]. POMC is first detected in the pituitary primordium at 24 hours post-fertilization and reaches peak concentration between the anterior and posterior domains at 48–64 hours post-fertilization [63, 67]. It is currently unknown whether corticotropic cell development depends on hypothalamic and CRH signaling. Since CRH, POMC, and ACTH transcripts are present at 48 hours post-fertilization, the hypothalamus and pituitary gland appear prepared to control interrenal cortisol production immediately after hatching and even to initiate a stress response if necessary [68].

One of the earliest markers of interrenal tissue development in zebrafish embryos is the expression of *ff1b* at 22 hours post-fertilization. This gene encodes a nuclear transcription factor and is a homolog of the mammalian steroidogenic factor 1 (SF1). The ligands of SF1 include sphingolipids and phospholipids. Interrenal differentiation requires *ff1b*, and this transcription

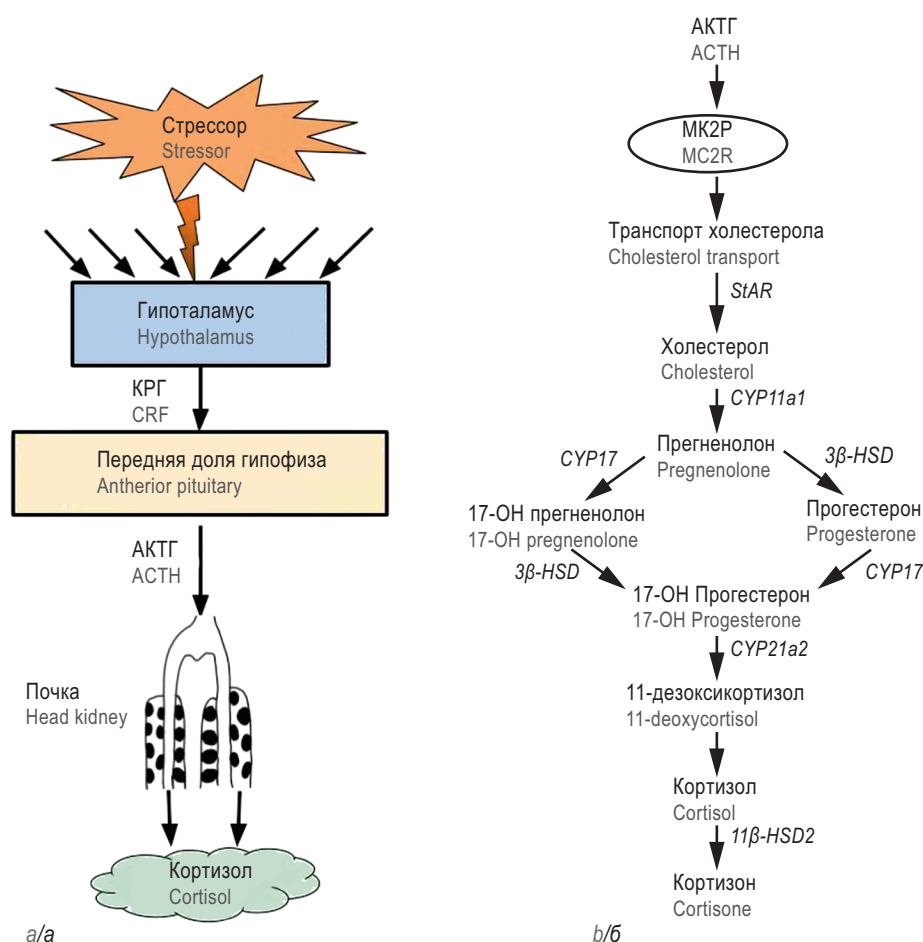


Fig. 2. Scheme of the HPA axis and cortisol synthesis: *a* — schematic representation of the hypothalamic-pituitary-adrenal axis and signaling cascade; *b* — cortisol synthesis in the interrenal cells is stimulated by the binding of ACTH to MC2R. MC2R — melanocortin-2 receptors; StAR — steroidogenic acute regulatory protein (adapted from [64])

Рис. 2. Схема строения ГГН-оси и синтеза кортизола: *a* — схематичное строение гипоталамо-гипофизарно-надпочечниковой оси и сигнального каскада; *б* — синтез кортизола в интерренальных клетках стимулируется связыванием АКТГ с MC2R. МК2Р — рецепторы меланокортина-2; StAR — стероидогенный острый регуляторный белок (StAR) (адаптировано из [64])

factor directly stimulates the expression of cytochrome P450 side-chain cleavage enzyme (P450_{scc}), which is the rate-limiting factor in steroidogenesis [65, 69].

Zebrafish eggs contain cortisol of maternal origin. This type of cortisol has also been observed in several other teleost species. A certain level of cortisol is believed to be necessary for embryonic development, as its *de novo* synthesis begins around the time of hatching [70]. However, the exact functions of cortisol during embryonic and early development have not been fully studied in any vertebrate. Although larvae are capable of synthesizing cortisol immediately after hatching, acute stress exposure does not cause an increase in cortisol levels during this period [64, 69, 71]. Since CRH is expressed in the preoptic area as early

as 24 hours after birth, the hypothalamus is capable of responding to stress signals early in development [70, 71].

It is not fully understood whether the period of stress hyporesponsiveness during embryogenesis and post-hatching is critical for development, especially given that cortisol has been shown to influence cranial development and somitogenesis in zebrafish [70, 72].

GC biosynthesis in zebrafish is fully functional at hatching [73]. More specifically, cortisol levels do not increase following exposure to a stressor at 25, 49, or 73 hours post-fertilization. The stress-induced cortisol reaction was first observed at 97 hours post-fertilization and 2 days after hatching. The absence



of a stressor-mediated response may not be due to the absence of MC2R, as transcripts of this receptor are elevated between 25 and 49 hours [65, 69, 74]. This suggests that insufficient signaling from higher centers (the pituitary gland and hypothalamus) may limit the activation of the cortisol stress axis during development in teleost fish. The presence of ACTH in the pituitary gland immediately after hatching suggests that the limiting factors may be located at the hypothalamic level.

Since CRH is also expressed in the preoptic area as early as 24 hours post-fertilization, the hypothalamus may be capable of responding to stress signals early in development. These observations suggest that the development of sensory gating in the hypothalamus, which is critical for stress perception and CRH release, may represent a temporally limiting factor in the delayed activation of the cortisol stress response during zebrafish development. However, it remains unclear whether this period is hyposensitive to stress during embryogenesis and critical for further development after hatching [64, 74].

In summary, the corticosteroid biosynthesis pathway becomes fully functional around the time of hatching in zebrafish. Furthermore, stress-related signals from the hypothalamus and pituitary gland (CRH and ACTH) can be detected at 48 hours post-fertilization [75, 76].

It cannot be concluded that the HPA axis is functionally mature at hatching, as the stress-mediated cortisol axis is not activated *in vivo* until two days later (97 hours after fertilization) [70, 77].

During embryonic development, GR transcript levels decreased between 1.5 and 25 hours post-fertilization, suggesting that GR signaling may not be critical during this period [72, 78]. However, from 49 hours post-fertilization onward, GR transcript levels recovered and stabilized. The increase in GR correlated with a greater capacity for cortisol synthesis during this period, suggesting that GR signaling may be critical for activation of the HPA axis after hatching [72, 73, 79].

Thus, genomic cortisol signaling plays a key role in metabolic organization and energy redistribution during the critical period of first feeding and growth in zebrafish development, as well as in stress regulation [74, 80]. This notion is supported by the increased tissue metabolic capacity and enhanced glucose me-

tabolism in response to genomic cortisol signaling in teleosts, as well as by the absence of a cortisol stress response before hatching [76, 77, 81].

In contrast to GR, MR transcript levels increased rapidly between 1.5 and 25 hours post-fertilization and continued to rise until 97 hours post-fertilization, suggesting that MR signaling is important for embryogenesis [78, 82]. Cortisol is a high-affinity ligand for MR, and for MR to be able to bind other ligands. It is co-expressed with 11 β -HSD2, an enzyme that metabolizes into cortisone. However, between 1.5 and 25 hours post-fertilization, very few 11 β -HSD2 transcripts are present in the embryo, indicating an inability of embryos to inactivate cortisol. Thus, maternal cortisol binding to MR may provide key signaling for zebrafish development, including the regulation of GR expression after hatching [64, 74, 80, 83].

Features of the hypothalamic-pituitary-adrenal axis in burrowing rodents

In humans, the main GC is cortisol. In burrowing rodents such as rats and mice, the principal GC is corticosterone, whereas, in humans, corticosterone is produced in minor quantities and human GRs have low affinity for it (Fig. 3). A similar pattern is observed in small mammals, in which corticosterone is the primary GC, and cortisol is present only in minor amounts [89, 90].

In mammals, glucocorticoid levels increase before the active phase of the circadian cycle. In humans, GC levels typically rise in the morning before awakening. In contrast, in nocturnal animals, GC levels increase in the evening, immediately before the onset of their nocturnal activity period. The increase in GC levels promotes the mobilization of the body's energy resources, required to sustain activity [91, 92].

In the body, corticosteroids are secreted in discrete pulses, forming an ultradian rhythm. Activation and inhibition of the HPA axis in rats regulate an approximately hourly cycle of corticosterone release. Signal transduction in response to corticosterone surges depends on dynamic interactions with GR and MR. It is generally accepted that the effects of low basal concentrations of endogenous GCs are mediated by MR due to their higher affinity. Low-affinity GRs play a key role at high concentrations of endogenous GCs (during stress or daily peaks of release) [28, 91]. It is

likely that optimal GC function is realized at their average concentrations, while hyper- and hyposecretion lead to negative consequences [30, 92, 93].

The HPA axis in rats operates through feedback regulatory interactions between the hypothalamus, pituitary gland, and adrenal glands (Fig. 4). Through the interaction of hypothalamic CRH and arginine-vasopressin (AVP), and the action of CRH on the CRH receptor (CRHR1), the production of pituitary ACTH is stimulated. ACTH, which is cleaved from POMC, stimulates the adrenal glands to produce corticosterone. Corticosterone binds to the glucocorticoid receptor (NR3C1) in the brain and suppresses the release of CRH through a negative feedback mechanism.

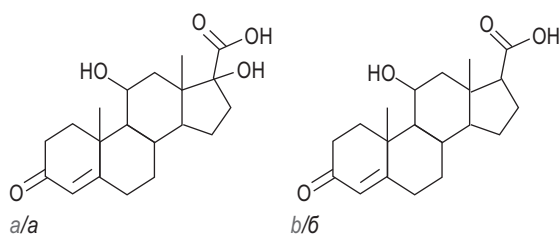


Fig. 3. Biochemical structure of cortisol (a) and corticosterone (b) (drawing by the authors)

Рис. 3. Биохимическая схема кортизола (а) и кортикостерона (б) (рисунок авторов)

FK506-binding protein 5 (FKBP5) alters receptor conformation and reduces the sensitivity of NR3C1 to corticosterone, thereby weakening negative feedback on the HPA axis. Oxytocin (OXT) slows the release of ACTH and corticosterone [94, 95].

The stress-hyporesponsive period (SHRP) is a distinctive feature of ontogenesis of the stress response in rats and mice. It is characterized by adrenal insensitivity to the trophic hormone ACTH and a reduced response to stressful stimuli, resulting in low and stable corticosterone levels. In mice, this period spans from 1 to 12 days, and in rats, from 4 to 14 days [96, 97].

This relative inactivity of the adrenocortical axis can be considered adaptive, as it limits catabolic processes initiated by circulating glucocorticoids and promotes the predominance of anabolic processes during neurodevelopment. Mothers begin to wean their pups at approximately 3 weeks of age, when the pup has fully emerged from the SHRP. At this time, pups exhibit a new, unique stress response: they are unable to rapidly terminate glucocorticoid secretion, resulting in high and sustained levels of circulating GCs and ACTH [40, 91, 98].

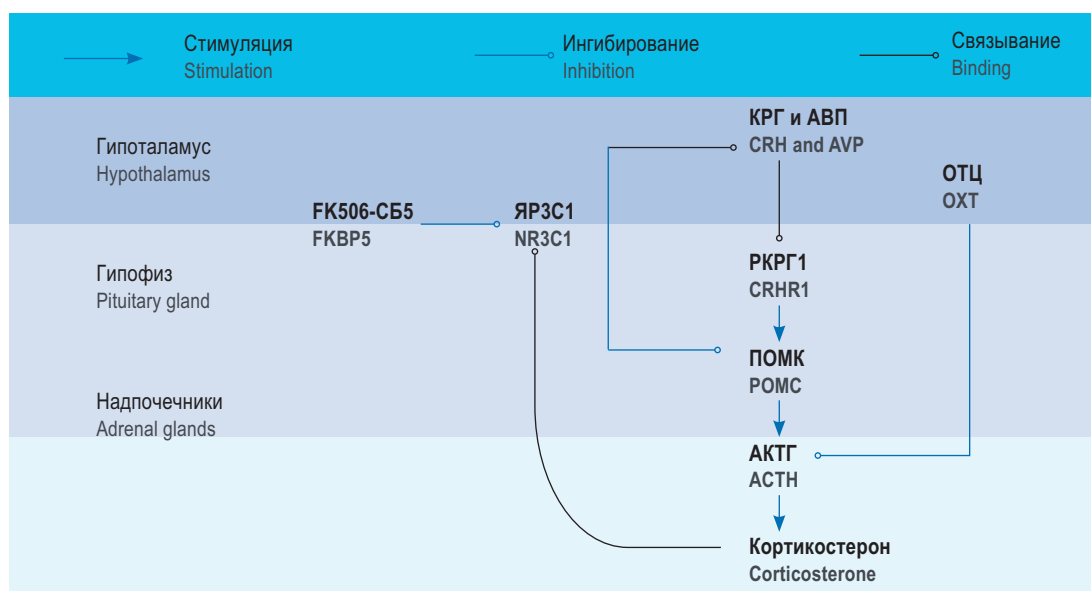


Fig. 4. Scheme of hypothalamic-pituitary-adrenal axis regulation in rats. AVP — corticotropin releasing hormone and arginine vasopressin; ACTH — adrenocorticotropin hormone; CRH — corticotropin releasing hormone; OXT — oxytocin; POMC — proopiomelanocortin; CRHR1 — CRH receptor; NR3C1 — nuclear glucocorticoid receptor; FKBP5-FK506 Binding Protein 5 (adapted from [96])

Рис. 4. Схема регуляции гипоталамо-гипофизарно-надпочечниковой оси у крыс. АВП — аргинин-вазопрессин; АКТГ — адренокортикотропный гормон; КРГ — кортикотропин-релизинг гормон; ОТЦ — окситоцин; ПОМК — проопиомеланокортин; ПКРГ1 — рецептор к кортикотропин-релизинг гормону 1; ЯРЗ-С1 — ядерный рецептор 3 группы С1; FK506-СБ5 — FK506-связывающий белок 5 (адаптировано из [96])



Events occurring during the SHRP can be either adaptive, leading to appropriate activation and rapid termination of the stress response, or maladaptive, resulting in long-term physiological changes that increase stress sensitivity and impair the ability to effectively terminate the stress response [96, 99].

Specific maternal behaviors regulate the stress response, e.g., breastfeeding suppresses corticosterone levels, while anogenital licking suppresses the ACTH stress response. Thus, in both rats and mice, maternal deprivation during the SHRP increases the stress reaction [44, 100, 101]. An increase in basal and stress-induced corticosterone levels is observed after 8 hours of separation, reaching the highest levels by 24 hours in both rats and mice [102]. For example, three 8-hour separations do not have a cumulative effect on corticosterone levels, as reunion with the mother restores them to control levels. After maternal deprivation, corticosterone and adrenocorticotrophic hormone levels remain elevated for at least 2 hours after a saline injection [8, 102, 103].

It is important to understand that in rats and mice, maternal presence is important not only for nutrition and thermoregulation. Certain maternal behaviors stimulate physiological processes in pups, such as heart rate, locomotor activity, the sleep-wake cycle, and growth hormone release, while inhibiting others, including the adrenocortical stress response [102, 104].

Understanding the mechanisms underlying the formation of a normal postnatal (limbic-)hypothalamic-pituitary-adrenal axis is essential for further studying stress-related disorders in early childhood, such as failure to thrive, weight loss, or depression [31, 105, 106].

When selecting a translational model, the sex of rats or mice should also be taken into consideration. Sex-dependent differences in GC action have been investigated by assessing the effect of GCs on genes expressed in the rat liver [107]. As a result, distinct sets of GC-regulated genes were identified, with specificity noted for females and males. Some genes were induced to a greater extent in males than in females, and vice versa. Analysis of the pathways regulating these genes showed that the anti-inflammatory effects of glucocorticoids were more pronounced in males. This difference was attributed to suppression of GC-

mediated anti-inflammatory signaling by ovarian hormones. Although these data relate specifically to sex differences in GC-mediated regulation of liver genes, similar mechanisms may also occur in other tissues and organs [108, 109].

TRANSLATIONAL ANIMAL MODELS FOR STUDYING STRESS RESPONSE REGULATION

Zebrafish as a translational model for stress research

Zebrafish have become a popular species in research laboratories for a number of reasons. These fish are asynchronous spawners, allowing them to be bred throughout the year and ensuring a constant supply of fertilized eggs. The zebrafish genome has been sequenced and is readily accessible. Several forward and reverse genetic approaches have been successfully proven in zebrafish, including transgenesis, gene silencing, and chemically induced mutagenesis.

Zebrafish also offer several advantages for studying the glucocorticoid stress axis. One large-scale study described zebrafish mutants that lack pituitary corticotroph cells and are therefore unable to synthesize ACTH [73, 77, 83, 84]. These mutants provide an excellent opportunity to study the role of ACTH in the stress response and the ability of fish to cope with stressors.

Although genome duplication specific to teleost fish provides opportunities to study evolution and compare different species, duplicated genes can also pose challenges for other areas of research. For example, when conducting gene silencing studies using morpholino oligonucleotides, it is important to consider that duplicated genes may require simultaneous silencing of both copies to fully suppress gene function [79, 85].

The use of zebrafish to study the effects of corticoids circumvents this problem, as zebrafish are currently the only fish known to possess single genes for all three components of the HPA axis, including CRH, ACTH, GR [64, 78, 84, 86].

The evolution of duplicated HPA axis components in zebrafish (a return to single-gene systems) endows zebrafish with a stress signaling cascade analogous to that of other vertebrates, including humans [74].



Zebrafish are widely used as a model organism for studying numerous human diseases and for drug research [75, 87]. For example, Barrett et al. (2006) used zebrafish as a model to investigate glucocorticoid-induced osteoporosis [76, 84].

Furthermore, Schaaf et al. (2008) describe another striking similarity between the corticoid systems of humans and zebrafish. Humans have two splice variants, GR α and GR β [77, 85, 88]. GR β does not bind classical agonists such as cortisol or dexamethasone, acts as a negative inhibitor of GR α , and is involved in various immune-related responses. The GR β variant has not been detected in animal model species to date, such as rats and mice. However, a GR β variant has been identified in zebrafish that has a similar structure, function, and expression pattern in adult tissues and during development [77, 80, 88]. These findings may represent an example of convergent evolution.

This discovery further confirms the advantage of zebrafish as a model for understanding the role of cortisol signaling in human diseases and stress-related disorders.

Burrowing rodents as a translational model for studying the effects of stress

Different stress characteristics, such as the duration, intensity, mode of exposure, and predictability, explain the spectrum of different responses to stress. Ultimately, the threshold at which the stress response shifts from physiological to pathological also depends on neuroendocrine, neurochemical, and genetic factors that determine individual differences in stress perception and the response. Given this, it seems logical that stress-modeling protocols should be adapted to the animal species and even the specific strain used when employing animal models [108, 110].

Although rats are widely used for modelling depression and other stress-associated disorders, mice have advantages. These include the availability of numerous genetically modified strains, such as transgenic and knockout mice, as well as lower maintenance costs compared with rats. In addition, susceptibility to stress varies depending on the mouse strain and the type of genetic modification, which should be considered when using rats and mice as translational models [110, 111].

For example, in modeling stress during early ontogenesis, differential effects of maternal deprivation on anxiety and depressive behavior have been demonstrated in different mouse strains. The C57Bl/6 strain appears to be more resilient to stress than other strains, such as the Balb/c strain [112, 113].

Thus, rats and mice are widely used as experimental animals in stress modeling and for improving our understanding of the biochemical and genetic mechanisms of many mental disorders: anxiety, depression, mood disorders, and addictions [114, 115]. These studies make a significant contribution to the investigation of treatment for these diseases. However, when selecting rats and mice as models, several factors should be considered. These include, for example, the specifics of the ultradian rhythm of corticosterone secretion, the timing of the GC rise, and the understanding of the necessity of maternal presence and its influence on the formation of the HPA axis. When selecting a species or strain, its sensitivity and susceptibility to a specific stressor should be considered, and the sex of the animal is also an important factor [116].

Principles for validation of translational models of zebrafish and burrowing rodents for stress research

Biochemical criteria

Different models are used to study cortisol levels under stress in zebrafish and burrowing rodents.

Cortisol levels in zebrafish are studied in models of acute stress using both physical methods and chemical stressors, both of which lead to an increase in cortisol levels. However, physiological differences between physical and psychological stress in zebrafish remain incompletely understood [117, 118].

In one model of acute stress in zebrafish, group 1 was subjected to physical stress — net chasing for 2 minutes, followed by a 15-minute waiting period before tissue collection; group 2 was subjected to space restriction in a specialized tube for 15 minutes; group 3 served as the control group. After 15 minutes of exposure to each stressor, the fish were decapitated, the brain tissue was removed, and the samples were immediately frozen in liquid nitrogen and stored at -80°C until cortisol extraction [119, 120].



In another model of chemical stress, the blood of conspecifics was used as the stressor in group 1 (5 ml per 10-liter aquarium with exposure for 15 minutes). The alarm pheromone of conspecifics was used in group 2 (1 ml per 10-liter aquarium for 15 minutes). The fish were then also decapitated and frozen until cortisol was extracted [118, 121–123].

When comparing physical and chemical stress groups, it was found that physical stress (net pursuit test, space restriction test) caused a more significant increase in cortisol levels than chemical stress. After the net pursuit test, cortisol levels increased fourfold compared to the chemical test [118].

To study serum cortisol levels in burrowing rodents, the following models are used [124].

In the study, male Wistar rats were divided into groups of 6 animals: group 1 — Porsolt forced swim test (FST); group 2 — restraint test (RT); group 3 — control group. All animals were of approximately the same weight. Differences in cortisol levels depending on the stress model were investigated. The experiment lasted 2 months, with tests conducted between 1:00 PM and 4:00 PM on weekdays.

In the FST group, a 15-cm-high Plexiglas cylinder filled with water at 25 °C was used, into which the animal was placed. Immobility was defined as the animal floating in the water in a slightly vertical position, making no movements other than those necessary to keep its head above the water surface. In the RT group, the animal was isolated for 3 hours in a transparent restraining tube measuring 21×7 cm [125]. Blood samples for determination of cortisol levels were collected from the animals during a fixed time interval before and after the procedure. As a result, following the FST, cortisol levels increased from a baseline of 76.22 ± 21.05 ng/mL to 121.64 ± 25.85 ng/mL; after the RT, serum cortisol levels were 133.85 ± 20.83 ng/mL. A significant increase in cortisol levels was observed after both tests. Similar results were observed in cases when FST was conducted until complete exhaustion in order to determine when stress acts as a stimulator and when, conversely, it leads to a decrease in physical endurance [124, 126, 127].

In the case of the RT, similar results were also obtained in other studies, for example, in a study where restraint lasted for 90 minutes [128].

However, when studying cortisol levels, one should also keep in mind the timing of blood collection and test administration. In the evening and at night, the activity period of burrowing rodents begins, during which basal cortisol levels are higher.

Physiological criteria

Stress reactions differ depending on the type of stressors applied (physical or psychological). In mammals, psychological stress (e.g., aversive environmental stimuli or predator-related cues), as well as physical stress (e.g., bleeding and infection) interacts with different neuronal and cellular structures in the brain. Under the influence of stressors, the sympathoadrenal system ensures rapid behavior adaptation, promoting alertness, vigilance, and behavior aimed at assessing the situation [129–134]. The HPA axis is activated later via the brainstem, with the paraventricular nucleus (PVN) of the hypothalamus activating or suppressing this axis [133].

Physical stressors also activate other brain structures that regulate autonomic responses to stress, including the nucleus of the solitary tract (NTS) and the dorsomedial hypothalamus (DMH) [135].

Like other vertebrates, various fish species exhibit robust physiological and behavioral responses to stress, the neurochemical and neuroendocrine mechanisms of which are similar to those in mammals [136, 137].

While zebrafish exposed to severe acute stress (e.g., 1-minute exposure to air) exhibit unchanged brain gene expression of interleukins (ILs) (IL-1 β and IL-6), brain-derived neurotrophic factor (BDNF), gamma interferon (IFN- γ), and tumor necrosis factor-alpha (TNF α), more severe acute stress (e.g., 90-minute exposure to cold water, bright light, vortex, shallow water, and restraint) enhances brain mRNA expression of all these genes [138]. Thus, these results show that stress reactions in fish and mammals are physiologically similar, especially because they are directly (and similarly) influenced by the type, intensity, frequency and duration of stress exposure.

In addition to GC synthesis, stress also causes the release of catecholamines from fish chromaffin cells, resulting in a rapid increase in blood glucose levels, as well as adrenaline and noradrenaline [137].



Stressors may also indirectly affect brain neuromediators, such as serotonin, dopamine and their metabolites, since in zebrafish subjected to acute isolation for 24 hours, an increase in serotonin levels and a decrease in the levels of its metabolite, 5-hydroxyindoleacetic acid, as well as dopamine and its metabolite, 3,4-dihydroxyphenylacetic acid, are observed [137, 138].

In addition to changes in the monoaminergic system, fish chromaffin cells also respond less to cholinergic stimulation after prolonged physical stress [139].

Along with the physiological similarities discussed above, there are also some interesting differences in the neurobiological responses of zebrafish to stress compared to mammals. For example, exposure to chronic stress in zebrafish leads to an increase in BDNF levels, which typically decrease (in most, but not all, brain regions) in response to chronic stress in rodents and humans, as well as in patients with affective disorders such as post-traumatic stress disorder, anxiety disorder, and depression [140–144]. In contrast, overexpression of BDNF in the brain produces anxiolytic and antidepressant effects in rodents, with similar therapeutic effects observed after increasing the dose of BDNF clinically [145].

The latter difference may result from the higher neuroprotective potential of the central nervous system (CNS) of fish (compared to the potentially more “fragile” CNS of mammals), which may also play a role during stress.

In zebrafish and humans, cortisol is produced in the adrenal glands during stress by 17- α hydroxylase, CYP17, an enzyme which is absent in rodents [146]. Some species differences in stress neuroendocrinology may play a role in how fish and rodents respond to acute and chronic stressors.

Anatomical criteria

Certain anatomical differences in brain morphology, particularly in the limbic system of mammals and fish, may also contribute to some differences in physiological and behavioral responses to stress in these species [147].

For example, acute restraint stress, a common stress protocol used to induce stress-related beha-

avior, differentially affects the limbic system, increasing CRH mRNA expression in the paraventricular nucleus in rats and decreasing it in zebrafish [148, 149]. Similarly, lesions of the anterior cingulate cortex and medial prefrontal cortex in rodents (structures that are absent in zebrafish) enhance ACTH and corticosterone secretion after restraint stress. Such effects cannot occur in zebrafish due to the absence of the prefrontal cortex [150].

Taken together, this suggests that neuromorphological differences between fish and mammals contribute to some distinct physiological and behavioral responses to stress.

Behavioral criteria

A number of physiological and behavioral stress reactions in fish and mammals also differ, e.g., in models based on early weaning [151]. While early maternal weaning stress increases anxiety-like behavior, hypothalamic CRH mRNA, and adult corticosterone levels in rodents, early social deprivation does not appear to affect baseline cortisol levels in adult zebrafish [152, 153]. Furthermore, maternal stress (4 days of maternal starvation) reduces cell proliferation in the forebrain of larval offspring at 5 days post-fertilization (DPF), and cortisol levels are elevated in 10-DPF embryos born to fasted mothers, indicating that maternal starvation stress induces changes in neurodevelopment in zebrafish.

In zebrafish, acute exposure to both physical and chemical stressors increases cortisol levels, inducing anxiety-like behavior. The presumed physiological differences between physical and psychological stressors remain poorly understood. Since these two types of stressors may activate different brain regions and various groups of GR/MR receptors, this could potentially lead to different behavioral and physiological responses depending on the stressor type [118, 154]. In mammals, behavioral responses to acute stress exposure are often described as the 3-F triad (fight, freeze, or flee), regulated by a cascade of stress responses involving limbic regions of the HPA axis.

It was proposed that the stress response in rodents may also induce characteristic grooming behavior as part of the “fight, freeze, flight, or groom” behavioral tetrad [155]. While the important role of

grooming in rodents and its development in stressful situations is widely recognized and likely represents an evolutionarily conserved trait across many species, fish appear to lack a clear analogous behavior [156].

Facial expression phenotypes in rodents have been linked to social activity, aggression, pain, well-being, and stress, suggesting that rodent facial expressions are also a potentially useful and sensitive biomarker of stress in mammals [157–159]. However, while mammals possess complex facial muscles, little is known about fish facial responses to stress, which requires further translational research [160].

Genetic criteria

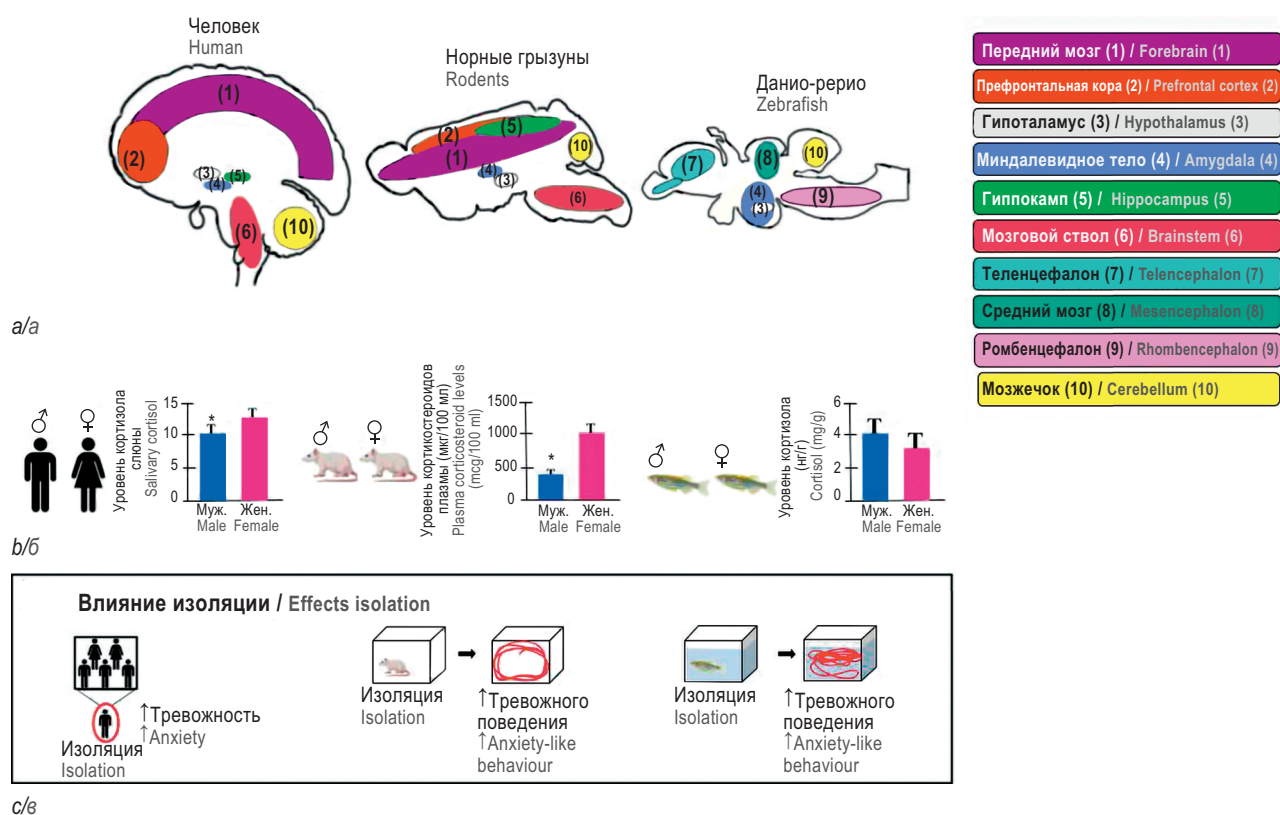
Since fish exhibit a high genetic homology of stress-related genes with their human and rodent counterparts (it is estimated that genetic sequence homology is 62–64% among zebrafish, humans, and

mice), several other common aspects of stress responses will be further analyzed and compared across the three species (Fig. 5) [161].

The major zebrafish genes associated with the stress response and their human and mouse orthologs are presented by the National Center for Biotechnology Information (NCBI) based on genetic testing, with the percentage of homology calculated on the basis of protein identification.

COMPARATIVE ANALYSIS OF TRANSLATIONAL MODELS OF ZEBRAFISH AND BURROWING RODENTS: ADVANTAGES AND LIMITATIONS

Table 1 presents a comparative analysis of the parameters of zebrafish and burrowing rodents that should be considered when selecting an optimal translational model for stress response research. Specifically, the characteristics of ontogenesis, HPA



c/в

Fig. 5. Comparison of stress status in humans, burrowing rodents and zebrafish: **a** — comparison of the location of the main structures of the brain; **b** — changes in cortisol levels in response to stress depending on gender; **c** — evaluation of behavioral effectiveness (adapted from [163])

Рис. 5. Сравнение реакции на стресс у человека, норных грызунов и Данио-рерио: **a** — сравнение расположения основных структур головного мозга; **б** — изменение уровня кортизола в ответ на стресс в зависимости от пола; **в** — влияние изоляции на поведение (адаптировано из [163])



axis development, accessibility, and anatomical, functional, and genetic aspects are discussed.

CONCLUSION

The study of the hypothalamic-pituitary-adrenal axis and the stress response, as well as the mechanisms of regulation, remains an important area of research. Reproducing such complex biochemical reactions and pathophysiological processes is impossible without the use of living organisms.

The approach to selecting a model depends on the aim of the study and the process that needs to be

recreated in the experiment. Thus, the selected organism should possess parameters and characteristics as similar as possible to those that need to be studied in humans.

When constructing a translational model, it is necessary to consider the biological, physiological, behavioral, and evolutionary features of the selected organism. An unjustified choice of model, without taking the above-mentioned features into account, leads to distorted results and subsequent difficulties in interpreting the obtained data. Such an approach to conducting research entails irrational financial and time costs, as well as the unjustified use of living resources.

Table 1

Key differences in the hypothalamic-pituitary-adrenal axis and stress response in zebrafish, rats, and mice (compiled by the authors)

Таблица 1

Основные различия в гипоталамо-гипофизарно-надпочечниковой оси и реакции на стресс у Данио-рерио, крыс и мышей (составлено авторами)

Критерий Criterion	Рыбы Данио-рерио Danio rerio fish	Норные грызуны (крысы и мыши) Burrowing rodents (rats and mice)
Особенности онтогенеза Features of ontogenesis	- В отличие от других рыб обладают лишь одной копией гена глюкокортикоидного рецептора, что позволяет изолированно изучать его функцию и реакцию на стрессор. - Unlike other fish, zebrafish possess only a single copy of the glucocorticoid receptor gene, allowing for the isolated study of its function and response to stressors. - Данио-рерио — единственная модель животных, обладающая вариантом сплайсинга глюкокортикоидного рецептора β со схожими структурой и паттерном экспрессии, присущими человеческому организму. - Zebrafish are the only animal model possessing a glucocorticoid receptor β splice variant with a similar structure and expression pattern to the human body	- Различия в действии глюкокортикоидов в зависимости от пола: обнаружены уникальные наборы генов, регулируемых глюкокортикоидами, при этом отмечалась специфичность для самок и самцов — одни гены были в большей степени индуцированы у самцов, чем у самок, и наоборот. - Sex-specific differences in glucocorticoid action: unique sets of glucocorticoid-regulated genes were identified, with specificity observed for females and males, with some genes being more induced in males than in females and vice versa
Первичный стрессовый гормон Primary stress hormone	Кортизол Cortisol	Кортикостерон Corticosterone
Особенности формирования гипоталамо-гипофизарно-надпочечниковой оси Features of the formation of the hypothalamic-pituitary-adrenal axis	- Секреция кортизола регулируется осью стресса, аналогичной таковой у млекопитающих. - Cortisol secretion is regulated by a stress axis similar to that found in mammals. - Связывание материнского кортизола с минералокортикоидным рецептором обеспечивает сигнализацию для развития Данио-рерио, включая регуляцию глюкокортикоидного рецептора после вылупления. - Maternal cortisol binding to the mineralocorticoid receptor provides signaling for zebrafish development, including regulation of the glucocorticoid receptor after hatching	- В организме глюкокортикоиды секретируются отдельными пиками, формируя ультрадианный ритм. Активация и ингибирование гипоталамо-гипофизарно-надпочечниковой оси у крыс регулирует приблизительно часовой цикл выброса кортикостерона. - In the body, glucocorticoids are secreted in discrete peaks, forming an ultradian rhythm. Activation and inhibition of the hypothalamic-pituitary-adrenal axis in rats regulates a roughly hourly cycle of corticosterone release. - Сигнальная трансдукция в ответ на пики выброса кортикостерона зависит от динамического взаимодействия глюкокортикоидного рецептора и минералокортикоидного рецептора [114]



Continuation of the Table 1 / Продолжение табл. 1

Критерий Criterion	Рыбы Данио-рерио Danio rerio fish	Норные грызуны (крысы и мыши) Burrowing rodents (rats and mice)
Ген глюкокортикоидного рецептора Features of the formation of the hypothalamic-pituitary-adrenal axis	Наличие единственной копии гена глюкокортикоидного рецептора имеет решающее значение для активации гипоталамо-гипофизарно-надпочечниковой оси после вылупления. The presence of a single copy of the glucocorticoid receptor gene is critical for the activation of the hypothalamic-pituitary-adrenal axis after hatching.	В геноме млекопитающих присутствует один ген глюкокортикоидного рецептора. Однако альтернативный сплайсинг дает изоформы глюкокортикоидного рецептора GR α (классический) и GR β , GR γ . The mammalian genome contains a single glucocorticoid receptor gene. However, alternative splicing produces glucocorticoid receptor isoforms GR α (classical) and GR β , GR γ .
Время развития функционально зрелой гипоталамо-гипофизарно-надпочечниковой оси Time of development of a functionally mature hypothalamic-pituitary-adrenal axis	Развитие механизмов восприятия стресса с дальнейшей активацией гипоталамо-гипофизарно-надпочечниковой оси происходит между 1-м и 5-м днями после оплодотворения. The development of stress perception mechanisms with further activation of the hypothalamic-pituitary-adrenal axis occurs between the 1st and 5th days after fertilization	- Экспрессия ГР начинается с раннего эмбриогенеза. У крыс экспрессия ГР начинается с раннего эмбриогенеза (с 12-го дня эмбриогенеза) во многих областях мозга. Минералокортикоидные рецепторы начинают экспрессироваться в конце беременности — за 3 дня до родов в области гиппокампа, гипоталамуса, четверохолмия, боковой перегородки, ствола, гипофиза. - GH expression begins early in embryogenesis. In rats, GH expression begins early in embryogenesis (from day 12 of embryogenesis) in many brain regions. Mineralocorticoid receptors expression begins at the end of pregnancy — 3 days before parturition — in the hippocampus, hypothalamus, corpora quadrigemina, lateral septum, brainstem, and pituitary gland. - У крыс КРГ достигает взрослого уровня экспрессии к концу постнатального дня 7. В гипоталамусе мыши экспрессия КРГ первоначально обнаруживается на 13-й день эмбриона и, аналогично крысам, снижается перед моментом рождения (эмбриональный день 17–18 у мышей), после чего следует увеличение экспрессии гормона до взрослого уровня. - In rats, CRH reaches adult levels of expression by the end of postnatal day 7. In the mouse hypothalamus, CRH expression is initially detected on embryonic day 13 and, similarly to rats, declines just before birth (embryonic days 17–18 in mice), followed by an increase in hormone expression to adult levels
Особенности формирования стресс-гипореактивного периода Features of the formation of the stress-hyporeactive period	Личинки способны синтезировать кортизол сразу после вылупления, но острое воздействие стресса не вызовет повышение уровня кортизола в этот период и, по некоторым данным, активируется <i>in vivo</i> в течение двух дней. Larvae are capable of synthesizing cortisol immediately after hatching, but acute stress exposure will not cause an increase in cortisol levels during this period and, according to some data, is activated <i>in vivo</i> within two days	- Характеризуется нечувствительностью надпочечников к АКТГ и более низкой реакцией на стрессовые раздражители, что приводит к низкому и стабильному уровню кортикостерона. - Characterized by adrenal insensitivity to ACTH and a reduced response to stressful stimuli, resulting in low and stable corticosterone levels. - У мышей этот период охватывает от 1 до 12 дней, а у крыс — от 4 до 14 дней. - In mice, this period lasts from 1 to 12 days, and in rats, from 4 to 14 days. - После окончания стресс-гипореактивного периода (момент начала отлучения от груди) демонстрируется уникальная реакция на стресс:



Continuation of the Table 1 / Продолжение табл. 1

Критерий Criterion	Рыбы Данио-рерио Danio rerio fish	Норные грызуны (крысы и мыши) Burrowing rodents (rats and mice)
		организм не способен быстро прекратить секрецию ГК, наблюдаются высокие и устойчивые уровни циркулирующих ГК и АКТГ. After the end of the stress-hyporesponsive period (the onset of weaning), a unique stress response is demonstrated: the body is unable to quickly cease glucocorticosteroid secretion, and high and stable levels of circulating corticosteroids and ACTH are observed.
Анатомо-функциональные особенности модели Anatomical and functional features of the model	- Надпочечник у млекопитающих гомологичен интерренальной железе у рыб - The adrenal gland in mammals is homologous to the interrenal gland in fish. - Гипоталамус и гипофиз на личиночных стадиях сформированы вдоль передней/задней оси в отличие от аналогичных структур у млекопитающих, которые сформированы вдоль дорсальной/вентральной оси. - The hypothalamus and pituitary gland in the larval stages are formed along an anterior/posterior axis, unlike their mammalian counterparts, which are formed along a dorsal/ventral axis. - Гипофиз Данио-рерио расположен ближе к гипоталамусу по сравнению с гипофизом млекопитающих. - The zebrafish pituitary gland is located closer to the hypothalamus than the mammalian pituitary gland. - Нейроны гипоталамуса, секретирующие кортикотропин-рилизинг-гормон, заканчиваются в передней доле гипофиза, в частности в областях кортикотропных и меланотропных клеток. - The hypothalamic neurons that secrete corticotropin-releasing hormone terminate in the anterior pituitary gland, specifically in the corticotropin and melanotropin cell regions	- Паравентрикулярные ядра у большинства млекопитающих трудно дифференцируются на отдельные цитоархитектонические компартменты. Однако у крыс возможно выделить приблизительно 10 отдельных групп перивентрикулярных ядер. Из них дорсальная часть медиальной парвицеллюлярной части содержит КРГ нейроэндокринные нейроны. - In most mammals, the paraventricular nuclei are difficult to differentiate into distinct cytoarchitectonic compartments. However, in rats, approximately 10 distinct groups of periventricular nuclei can be identified. Of these, the dorsal portion of the medial parvicellular portion contains CRH neuroendocrine neurons.
Доступность Availability	- Асинхронные нерестники (вид разводят в течение всего года с поддержанием постоянного числа оплодотворенных яиц). - Asynchronous spawners (the species breeds year-round, maintaining a constant number of fertilized eggs). - Геном секвенирован, хорошо изучен, доступен для генетических модификаций. - The genome has been sequenced, is well-studied, and is accessible for genetic modification	- Существует множество генетически модифицированных штаммов, таких как трансгенные и нокаутные мыши. - There are many genetically modified strains, such as transgenic mice and knockout mice. - Более низкие затраты на содержание мышей по сравнению с крысами. - Mice are less expensive to maintain than rats. - В зависимости от штамма/вида мышей, отличается их восприимчивость к стрессовым воздействиям. - Depending on the strain/species of mice, their susceptibility to stress varies
Специфичность Specificity	Возможно получение мутантов для изучения механизмов работы гипоталамо-гипофизарно-надпочечниковой оси (рыбы-мутанты, у которых отсутствуют гипофизарные кортикотропные клетки, следовательно, отсутствует АКТГ)	Подъем уровня глюкокортикоидов происходит вечером, непосредственно перед началом периода ночной активности (для человека подъем глюкокортикоидов характерен утром, до пробуждения)



Ending of the Table 1 / Окончание табл. 1

Критерий Criterion	Рыбы Данио-рерио Danio rerio fish	Норные грызуны (крысы и мыши) Burrowing rodents (rats and mice)
	- It is possible to create mutants to study the mechanisms of the hypothalamic-pituitary-adrenal axis (mutant fish that lack pituitary corticotropic cells and therefore lack ACTH). - Единственная в настоящее время известная рыба, обладающая одним геном для всех трех компонентов гипоталамо-гипофизарно-надпочечниковой оси — кортикотропин-рилизинг-гормона, АКТГ, глюкокортикоидного рецептора. - The only currently known fish possessing a single gene for all three components of the hypothalamic-pituitary-adrenal axis — corticotropin-releasing hormone, ACTH, and the glucocorticoid receptor	- Glucocorticoid levels rise in the evening, immediately before the onset of nocturnal activity (in humans, glucocorticoid levels typically rise in the morning, before waking). - Специфическое материнское поведение регулирует реакцию на стресс (например, кормление грудью подавляет уровень кортикостерона). - Specific maternal behaviors regulate the stress response (for example, breastfeeding suppresses corticosterone levels)

Note: ACTH — adrenocorticotrophic hormone; GR — glucocorticoid receptor; CRH — corticotropin-releasing hormone.

Примечание: АКТГ — аденокортикотропный гормон; ГР — глюкокортикоидный рецептор; КРГ — кортикотропин-рилизинг-гормон.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Experiments with animals were carried out in accordance with international rules (Directive 2010/63/EU of the European Parliament and of the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes).

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Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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Comparative characteristics of new benzimidazole derivatives with potential analgesic properties

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ABSTRACT. Introduction. The development of novel highly effective analgesics represents a critical objective due to the high prevalence of pain syndrome as a component of various pathological conditions, which significantly impairs patients' quality of life. **Aim.** The study aimed to investigate the duration of action of two novel opioid analgesics, determine their median lethal (LD_{50}) and median effective (ED_{50}) doses, and calculate their therapeutic indices. **Materials and methods.** The analgesic activity was assessed using the Tail Flick test. The ED_{50} was determined based on the results of an additional Tail Flick assay. To estimate the LD_{50} , the test compounds were administered at doses exceeding the previously determined ED_{50} by more than 100-fold. The therapeutic index was calculated as the ratio of LD_{50} to ED_{50} . **Results.** For compound BIF-70, the ED_{50} was 0.7854 mg/kg, the LD_{50} was 304.3 mg/kg, and the therapeutic index was 387.45. For BIF-72, the ED_{50} was 0.5852 mg/kg, the LD_{50} was 331.4 mg/kg, and the therapeutic index was 566.3. The duration of analgesic action for both compounds was at least 150 minutes at doses ranging from 1 to 10 mg/kg. **Discussion.** The duration of action of the studied compounds was comparable to that of classical opioid analgesics. The LD_{50} values for both substances were consistent with those of conventional opioids. Notably, the therapeutic indices of BIF-70 and BIF-72 significantly exceeded that of morphine, though they remained lower than that of butorphanol. **Conclusions.** Both compounds demonstrate promising pharmacological profiles as potential opioid analgesics and warrant further preclinical investigation.

Keywords: benzimidazole derivatives, opioid analgesics, behavioral tests, analgesic activity, pharmacokinetic parameters, therapeutic index

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Сравнительная характеристика новых производных бензимидазола с потенциальными анальгетическими свойствами

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РЕЗЮМЕ. Введение. Создание новых высокоэффективных анальгетиков представляется важной задачей в связи с распространенностью болевого синдрома как компонента различных патологий, значительно ухудшающего качество жизни пациентов. **Цель.** Изучить длительность действия двух новых опиоидных анальгетиков, определить значения их полулетальной (LD_{50}) и полуэффективной (ED_{50}), доз а также установить условный терапевтический индекс. **Материалы и методы.** Исследования анальгетической активности проводились на установке Tail Flick. Определение значения полуэффективной дозы проводилось на основании результатов дополнительного теста Tail Flick. Для расчета полулетальной дозы исследуемые вещества вводились в дозах, превышающих рассчитанную на предыдущем шаге полуэффективную более чем в 100 раз. На основании данных показателей рассчитывался интегральный терапевтический индекс. **Результаты.** Для соединения BIF-70 полуэффективная доза составила 0,7854 мг/кг, полулетальная — 304,3 мг/кг, условный терапевтический индекс — 387,45. Для BIF-72 полуэффективная доза составила 0,5852 мг/кг, полулетальная — 331,4 мг/кг, условный терапевтический индекс — 566,3. Длительность действия изученных соединений составляет не менее 150 минут при дозировках от 1 до 10 мг/кг. **Обсуждение.** Длительность действия незначительно отличается от классических опиоидных анальгетиков. Величина полулетальной дозы обоих соединений в целом соответствует классическим анальгетикам. Значение терапевтического индекса как BIF-70, так и BIF-72 заметно превосходит аналогичный параметр морфина, но уступает буторфанолу. **Выводы.** Оба соединения можно рассматривать в качестве перспективных кандидатов опиоидных анальгетиков и рекомендовать их к дальнейшему доклиническому изучению.

Ключевые слова: производные бензимидазола, опиоидные анальгетики, поведенческие тесты, анальгетическая активность, фармакокинетические показатели, терапевтический индекс

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования

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INTRODUCTION

The development of new safe and effective analgesics is a priority for experimental pharmacology [1] due to the large number of conditions accompanied by pain, as well as the sharp rise in opioid abuse and the increase in associated overdose deaths, which have led to the opioid crisis [2]. It is precisely the threat of the continued escalation of the opioid epidemic that makes it urgent to change the strategy and substantially revise the structure of medical use of potent opioid analgesics, such as morphine. These agents are characterized by unfavorable pharmacokinetic properties and a low therapeutic index, necessitating significantly higher therapeutic doses (relative to their high affinity for CNS opioid receptors), exhibit abuse liability, and lead to pronounced adverse effects, including those life-threatening and detrimental to patient health [3].

To overcome the challenge of abuse liability in new analgesics, the search among selective opioid receptor agonists, in particular kappa-agonists — long recognized as analgesics with low abuse potential — appears promising [4]. However, their use may be associated with the development of serious kappa-mediated psychotropic adverse effects, including dysphoria, anhedonia, and hallucinations. The mechanism underlying these effects involves signal transduction via the β -arrestin-2 intracellular signaling cascade with activation of mitogen-activated protein kinase — p38-MAPK, as opposed to analgesia mediated by $G\alpha_{i/o}$ protein activation [5]. This fact suggests the therapeutic potential of G protein-biased kappa-opioid receptor ligands as analgesics devoid of dysphoric side effects.

Previous studies conducted at the Department of Pharmacology and Bioinformatics of Volgograd State Medical University (VolgSMU) included targeted *in vitro* screening of benzimidazole-based polycyclic derivatives synthesized at the Research Institute of Physical and Organic Chemistry of Southern Federal University (RIPOC SFU, Rostov-on-Don) [6]. These efforts identified a number of compounds with high selectivity for kappa-opioid receptors [7]. Analysis of the core scaffolds of the experimentally tested substances demonstrated that 2,9-disubstituted imidazo[1,2-*a*]benzimidazoles represent a promising class of compounds for the discovery of structurally novel kappa-agonists with

potentially high kappa-receptor selectivity. Moreover, the kappa-agonist properties of derivatives in this class largely depend on the nature of the substituent at the key nitrogen atom in position 9 and the structure of the moiety at the second position of the heterocyclic core. In the latter case, the presence of a phenyl ring at the C² position of the tricyclic system is decisive, while the introduction of halogen atoms, particularly fluorine, into the phenyl ring statistically significantly increases the efficacy of the studied compounds [8]. The most promising compound — a fluorophenyl derivative of [1,2-*a*]-imidazobenzimidazole [9] — exhibits pronounced analgesic activity (superior to butorphanol and morphine in *in vivo* experiments), and docking analysis revealed that its binding energy to the catalytic domain of p38-MAPK is high and comparable to that of the reference p38-MAPK inhibitor SB203580. The ability of this compound to inhibit p38-MAPK was assessed in a conditioned place avoidance test following systemic administration [10].

The fact that selective p38-MAPK inhibitors belong to the class of fluorophenyl derivatives of imidazole systems [11, 12] provides a rationale for incorporating these moieties into new molecules in order to develop structurally novel kappa-receptor agonists with p38-MAPK inhibitory properties. These findings prompted further search for compounds with a specified pharmacological activity profile, which led to the identification [13] of two lead compounds exhibiting the most pronounced analgesic effects and selected for evaluation of certain pharmacokinetic and toxicological parameters.

AIM

The aim of this study was to assess the duration of action of the novel opioid analgesics with laboratory codes BIF-70 and BIF-72, to determine their median lethal (LD₅₀) and median effective (ED₅₀) doses, and to determine their therapeutic index (TI).

MATERIALS AND METHODS

The study was performed on adult non-inbred male mice weighing 23–28 g, obtained from the Rappolovo Laboratory Animal Breeding Facility of the Russian Academy of Medical Sciences (Saint Petersburg, Russia). During the experimental period, mice were housed



in groups of 10 with unrestricted access to water and food, under a regulated light/dark cycle (12/12 h, lights on at 8:00 AM) and at a temperature of 20–22 °C. All animal procedures were carried out in compliance with national and international legal and ethical regulations. National requirements were met in accordance with Decree No. 51 of August 29, 2014, approving Sanitary Regulations and Standards SP 2.2.1.3218-14 "Sanitary and Epidemiological Requirements for the Design, Equipment, and Maintenance of Experimental Biological Clinics (Vivariums)". International standards were followed as specified in Directive 2010/63/EU of the European Parliament and of the Council of September 22, 2010, on the protection of animals used for scientific purposes. The experiments were approved by the Regional Research Ethics Committee of Volgograd Region (registration number IRB 00005839, IORG 0004900 (OHRP); protocol No. 2077-2018 dated October 30, 2018).

The compounds BIF-70 and BIF-72 are 2-(2'-fluoro-[1,1'-biphenyl]-4-yl)-3-methyl-9-(2-(pyrrolidin-1-yl)ethyl)-9H-benzo[d]imidazo[1,2-a]imidazole and 4-(2-(2'-fluoro-[1,1'-biphenyl]-4-yl)-3-methyl-9H-benzo[d]imidazo[1,2-a]imidazol-9-yl)ethyl)morpholine, respectively. They were used as bulk substances synthesized at the Research Institute of Physical and Organic Chemistry of Southern Federal University, Rostov-on-Don.

Analgesic activity was assessed using a Tail Flick apparatus (Ugo Basile S.r.l., Varese, Italy) at 55 % irradiation intensity in male mice. Group sizes and allocation were determined according to the experimental conditions. Animals were randomly assigned to groups; baseline values were recorded for each animal prior to substance administration.

Analgesic activity was assessed based on the increase in nociceptive response latency to a painful stimulus (infrared irradiation) [14]. Animals were placed in a restraining tube for habituation to the novel environment 5 minutes prior to testing. The nociceptive response was defined as tail withdrawal from the stimulus source. The painful stimulus was applied four times per animal. Response latency was recorded using the built-in software of the apparatus. The maximum exposure time to infrared irradiation was 15 s [15].

The compounds were dissolved in distilled water and administered intraperitoneally.

To study the duration of action of the compounds, the experiment was performed on 40 animals divided

into 4 groups according to the dose of the test compound. Measurements were taken 30 minutes after substance administration and then repeated every 30 minutes over a 3-hour period for each animal. For each animal, the mean latency $\pm$ standard error of the mean (SEM) was calculated.

To construct time–effect curves, the relative change in response ($\Delta\%$) was calculated. The magnitude of the effect was assessed by comparing the absolute response time of animals before substance administration and during the plateau phase, which was determined based on the preceding calculations.

To determine the ED₅₀, an additional Tail Flick test was performed using the same protocol in a group of 40 male mice divided into 4 subgroups according to the dose of the administered compound. The magnitude of the effect was again assessed during the plateau phase, as defined previously.

To calculate the LD₅₀ of each compound, 40 animals were randomized into four groups and received the test compounds at doses of 100, 250, 350, and 500 mg/kg. Mortality was assessed 24 hours after administration.

The therapeutic index was calculated based on these parameters using the following formula:

$$\text{Therapeutic index} = \frac{\text{LD}_{50}}{\text{ED}_{50}}.$$

Data were analyzed using two-way ANOVA followed by Fisher's least significant difference (LSD) test. Graph plotting and statistical calculations, including ED₅₀ and LD₅₀ estimation, were performed using GraphPad Prism 8 software with its built-in tools.

RESULTS

The study of effect duration demonstrated that a pronounced analgesic effect developed within 30 min, forming a plateau that persisted on average from the 60th to the 90th minute, followed by a steady decline in analgesic activity. Figures 1 and 2 show individual time–effect curves for the tested compounds. Figure 3 presents the distribution of individual effect values during the plateau phase.

A statistically significant difference from the control group was maintained:

- for BIF-70 at 1 mg/kg — until the end of the observation period;
- for BIF-70 at 10 mg/kg — until the 150th minute;

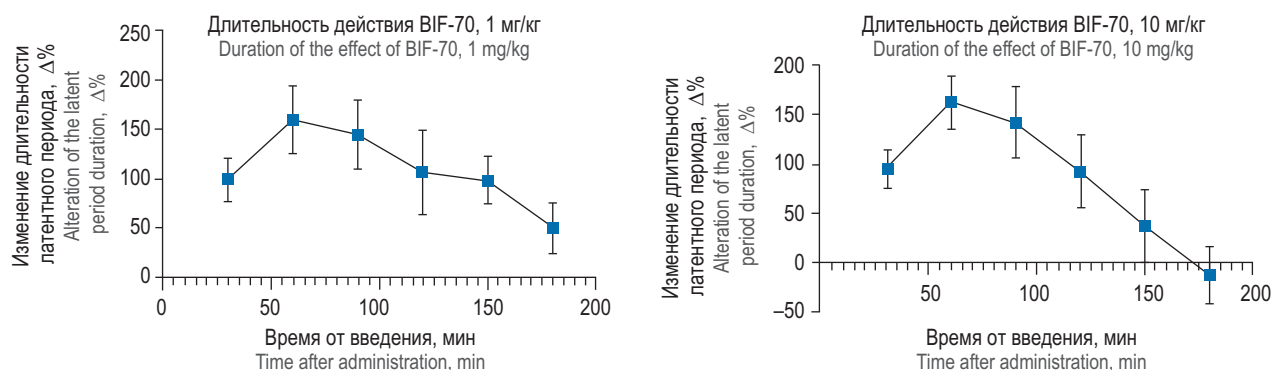


Fig. 1. Time-dependent changes in the effect intensity of BIF-70 (1 and 10 mg/kg, intraperitoneal) (drawing by the authors)

Рис. 1. Изменение выраженности эффекта соединения BIF-70 (1 и 10 мг/кг, внутривенно) во времени (рисунок авторов)

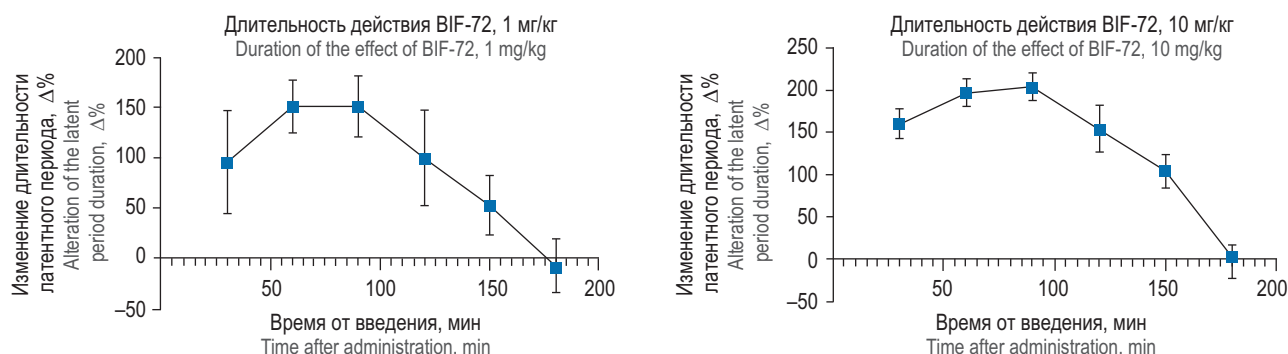


Fig. 2. Time-dependent changes in the effect intensity of BIF-72 (1 and 10 mg/kg, intraperitoneal) (drawing by the authors)

Рис. 2. Изменение выраженности эффекта соединения BIF-72 (1 и 10 мг/кг, внутривенно) во времени (рисунок авторов)

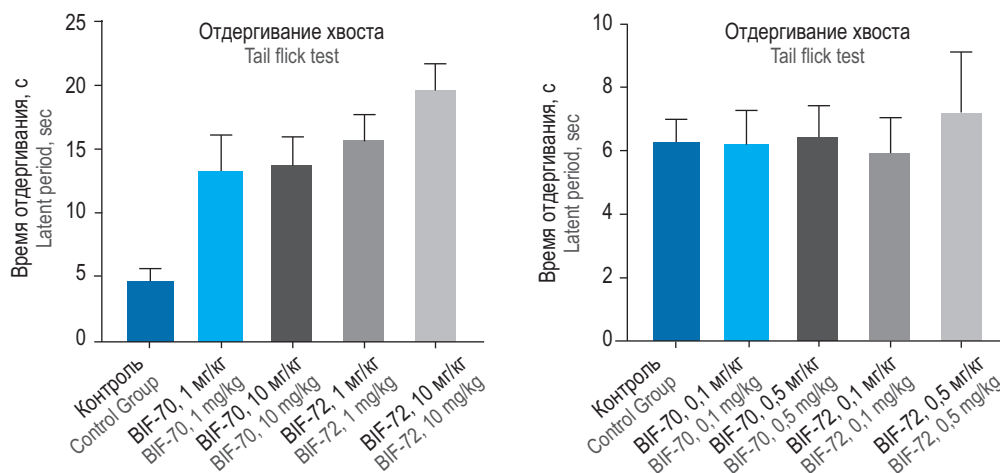


Fig. 3. Comparison of the effect magnitude of the studied compounds at different concentrations during the plateau phase (60–90 min post-administration) (drawing by the authors)

Рис. 3. Сравнение выраженности эффекта изучаемых соединений в различных концентрациях в фазе «плато» (60–90 минут от введения) (рисунок авторов)

- for BIF-72 at 1 mg/kg — until the 150th minute;
- for BIF-72 at 10 mg/kg — until the 150th minute.

The analgesic activity of the studied compounds at different doses was then assessed during the plateau phase. The results are shown in Figure 3 (left).

It should be noted that the differences between BIF-70 (1 and 10 mg/kg) and BIF-72 (1 mg/kg) were

not statistically significant. At the same time, BIF-72 (10 mg/kg) showed a modest but statistically significant superiority over the other groups..

Thus, the prolongation of reaction time during the plateau phase for these doses was as follows:

- for BIF-70 at 1 mg/kg — $162 \pm 38.58\%$;
- for BIF-70 at 10 mg/kg — $153.75 \pm 27.69\%$;

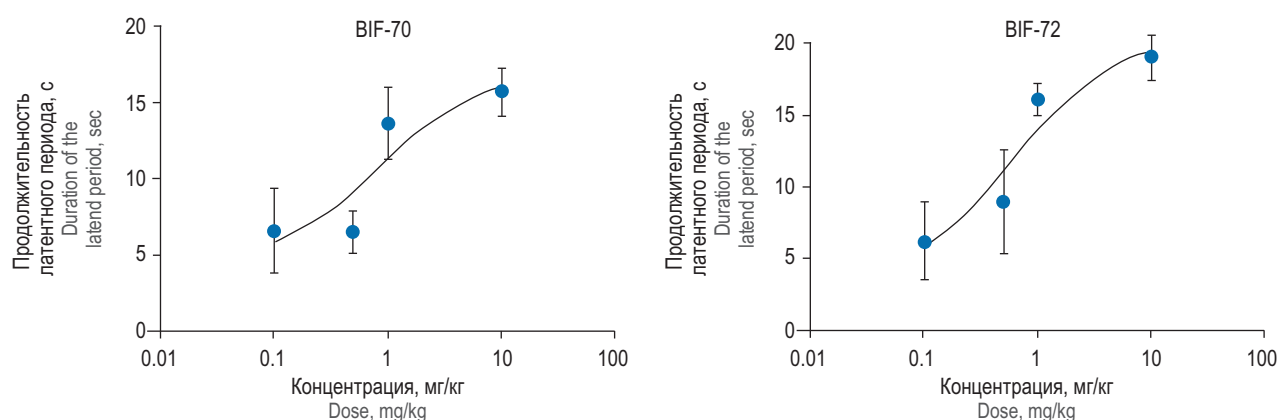


Fig. 4. Dose-response curves for compounds BIF-70 (left; $ED_{50}=0.7854$ mg/kg, 95% CI 0.4544–1.383, $R^2=0.64$) and BIF-72 (right; $ED_{50}=0.5852$ mg/kg, 95% CI 0.3793–0.8878, $R^2=0.77$): CI — Confidence interval; ED_{50} — median effective dose; R^2 — coefficient of determination (drawing by the authors)

Рис. 4. График эффективности соединений BIF-70 (слева; $ED_{50}=0,7854$ (95% ДИ 0,4544–1,383) мг/кг, $R^2=0,64$) и BIF-72 (справа; $ED_{50}=0,5852$ (95% ДИ 0,3793–0,8878) мг/кг, $R^2=0,77$): ДИ — доверительный интервал; ED_{50} — полуэффективная доза, R^2 — коэффициент детерминации (рисунок авторов)

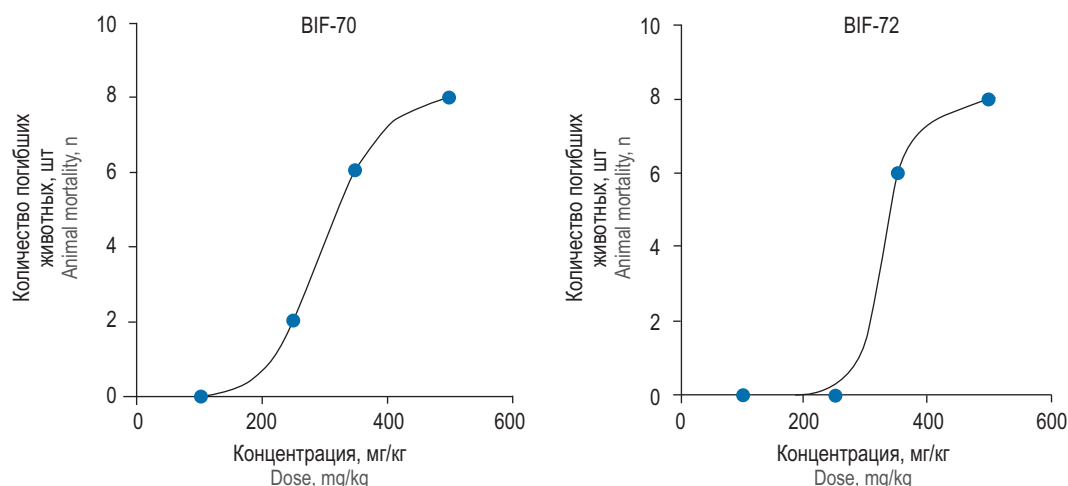


Fig. 5. Dose-response toxicity curves for compounds BIF-70 ($LD_{50}=304.3$ mg/kg, $R^2=0.86$, TI=387.45) and BIF-72 ($LD_{50}=331.4$ mg/kg, $R^2=0.76$, TI=566.3): TI — therapeutic index; LD_{50} — median lethal dose; R^2 — coefficient of determination (drawing by the authors)

Рис. 5. Токсичность соединений BIF-70 ($LD_{50}=304,3$ мг/кг, $R^2=0,86$, ТИ=387,45) и BIF-72 ($LD_{50}=331,4$ мг/кг, $R^2=0,76$, ТИ=566,3): ТИ — терапевтический индекс, LD_{50} — полуметальная доза; R^2 — коэффициент детерминации (рисунок авторов)

- for BIF-72 at 1 mg/kg — $159.45 \pm 23.8\%$;
- for BIF-72 at 10 mg/kg — $206.02 \pm 16.67\%$.

Regarding the activity of BIF-70 and BIF-72 at lower doses (0.1 and 0.5 mg/kg), no statistically significant differences were observed between any of the groups, including the control group (Fig. 3, right).

Based on the obtained data, dose-response curves were plotted (Fig. 4), and the ED_{50} values were calculated.

Subsequently, the LD_{50} and therapeutic index were determined for the compounds. The results are presented in Figure 5. None of the doses used resulted in complete lethality in any experimental group; ho-

wever, an LD_{50} was achieved, which was interpreted as a satisfactory level of lethality.

DISCUSSION

The present study demonstrated that the duration of action of the tested compounds is approximately 150 min at doses ranging from 1 to 10 mg/kg. In comparison, butorphanol at similar doses exhibits its most pronounced effect within 60 to 120 min [16]. This time frame closely corresponds to the plateau phase observed for BIF-70 and BIF-72. The magnitude of the analgesic effect



is not discussed here, as it was the subject of a separate publication [13].

Regarding median effective and median lethal doses, previous studies have reported LD₅₀ values for classical analgesics in mice after intraperitoneal administration. For butorphanol, the LD₅₀ is 192 mg/kg (therapeutic index 192,000 in the tail-flick test) [17]. For morphine, the LD₅₀ is 400 mg/kg [18] (therapeutic index 100) [19].

Thus, the median lethal dose of both compounds is generally comparable to that of classical analgesics. However, their therapeutic index is considerably lower than that of butorphanol, which may raise concerns regarding their further clinical prospects. Nevertheless, it should be noted that the therapeutic index of the studied compounds is 4–5 times higher than that of morphine — a drug that remains clinically relevant.

Furthermore, previously reported findings [13] indicate that the analgesic activity of BIF-70 and BIF-72 in various experimental models is comparable to that of butorphanol, with BIF-72 exhibiting neither reinforcing nor dysphoric effects. Moreover, this compound markedly suppressed inflammatory pain responses in specific tests.

The differences in the properties of the studied compounds, as well as in their analgesic activity levels, may result from distinct degrees of affinity for kappa-opioid receptors and possible differences in their effects on post-receptor signaling pathways. Indeed, BIF-72 has previously been shown to exhibit more pronounced agonistic activity at kappa-opioid receptors, which was abolished by a specific antagonist [20]. This mechanism of action may presumably be related to the presence of a hydrogenated six-membered heterocycle linked to the N⁹ atom in the compound structure. In the above-cited publication, researchers from the Research Institute of Physical and Organic Chemistry of Southern Federal University proposed further investigation of the properties of 2-arylimidazo[1,2-a]benzimidazoles, with the ultimate goal of developing more effective analgesics.

CONCLUSIONS

In summary, the obtained data collectively suggest that BIF-70 and BIF-72 represent promising opioid analgesics and warrant further preclinical evaluation. Such studies should include docking analysis to elucidate their mechanism of action, as well as investigation of

their metabolism and chronic (including organ-specific) toxicity to enable a more refined safety assessment.

With regard to further investigation of analgesic properties per se, the most promising direction involves studies assessing the effects of the compounds on somatic pain — a modality for which effective relief is characteristic of opioidergic agents. Additionally, as noted in a previous report [13], BIF-72 exerted a pronounced effect during the second phase of the formalin-induced pain model, which may be interpreted as evidence of anti-inflammatory activity; however, this finding requires more detailed investigation and independent confirmation.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Animal manipulations were carried out in compliance with legal and ethical standards (Resolution of 29.08.2014 No. 51 “On approval of SP 2.2.1.3218-14 “Sanitary and epidemiological requirements for the design, equipment and maintenance of experimental biological clinics (vivariums)”; Directive of the European Parliament and of the Council of the European Union 2010/63/EU of 22 September 2010 “On the protection of animals used for scientific purposes”).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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Agrelax reduces conditioned place preference of ethanol and compulsive behavior in rats during its withdrawal

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ABSTRACT. Introduction. Among the orexigenic peptides that mediate the emotional effects of psychoactive substances, the peptide hormone ghrelin attracts attention. It was shown that the ghrelin receptor antagonist agrelax, synthesized at the Institute of Experimental Medicine, reduced the manifestations of compulsive overeating and impulsivity in a model of gambling addiction. **Aim.** To study the effect of agrelax on the conditioned place preference of ethanol and compulsive behavior against the background of its withdrawal in male rats. **Materials and methods.** A conditioned place preference of ethanol was developed in male rats in a two-chamber setup, over a period of eight days, for two hours per day. In the first hour, the rats were placed in the first chamber and administered saline solution. Then, ethanol (0.5 g/kg) was administered intraperitoneally and the rats were placed in the second compartment of the setup for 1 hour. On the 9th day, the doors between the compartments were opened, and the rat test groups were administered either agrelax (10 µg in 20 µL) intranasally, naloxone (1 mg/kg) intraperitoneally, or simple saline, and the animal was placed in the setup for 10 min. Then, place preference extinction was carried out for seven days, which consisted of daily testing without the introduction of alcohol and other drugs. On the 11th day of the experiment, compulsive behavior was recorded by burying marbles in the marble test after the introduction of each of the substances. On the 18th day of the experiment, ethanol was administered and the resumption of the conditioned place preference reaction was recorded. Some animals were administered agrelax or naloxone 5 minutes before the introduction of ethanol to determine the effect on the resumption of the conditioned place preference reaction. **Results.** After the introduction of saline on the 8th day of the experiment, the animals spent 71% of the time in the chamber associated with the introduction of ethanol. In rats given agrelax or naloxone, a decrease in staying in the chamber associated with ethanol was observed, respectively, to 45% ($p < 0.05$) and 39% ($p < 0.01$). Naloxone caused a blockade of the renewal of preference for the ethanol chamber, which was manifested by a 26% decrease in the time spent in the preferred chamber associated with the introduction of ethanol. The ghrelin receptor antagonist agrelax (10 µg in 20 µL, intranasally) did not cause a decrease in the reproduction of the conditioned reaction of preference for the ethanol chamber. On the 10th day of the experiment, after the introduction of saline, the animals buried 17.2 ± 2.3 marbles in the marble test. Agrelax and naloxone reduced the number of buried marbles against the background of ethanol withdrawal to 13 ± 3.5 ($p < 0.05$) and 11 ± 2.4 ($p < 0.05$), respectively. **Conclusion.** Agrelax reduces the manifestation of the conditioned reaction of ethanol place preference and compulsive behavior in rats against the background of its withdrawal, which is comparable to the effect of naloxone. At the same time, unlike naloxone, agrelax did not cause a decrease in the resumption of ethanol place preference. Thus, we demonstrate the important role of the ghrelin system in the mechanisms of the reinforcing effect of alcohol, which invites further investigation into the use of new ghrelin antagonists in the correction of pathological craving.

Keywords: ghrelin, agrelax, conditioned reaction of place preference, alcohol, compulsivity

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Оригинальная статья

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Агрелакс снижает условную реакцию предпочтения места этанола и компульсивное поведение крыс на фоне его отмены

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РЕЗЮМЕ. Введение. Среди орексиогенных пептидов, опосредующих эмоциональные эффекты психоактивных веществ, привлекает внимание пептидный гормон грелин. Показано, что антагонист рецептора грелина агрелакс, синтезированный в ФБГНУ «Институт экспериментальной медицины», снижал проявления компульсивного переедания и импульсивности в модели игровой зависимости. **Цель.** Изучить влияние агрелакса на условную реакцию предпочтения места введения этанола и компульсивное поведение на фоне его отмены у самцов крыс. **Материалы и методы.** У самцов крыс вырабатывали условную реакцию предпочтения места введения этанола в двухкамерной установке. В течение 8 дней вводили физиологический раствор и помещали животное в отсек установки на 1 ч. Через 2 ч вводили этанол (0,5 г/кг внутривентрально) и производили посадку в другой отсек установки на 1 ч. На 9-й день открывали дверцы между отсеками, вводили вещество (агрелакс 10 мкг в 20 мкл интраназально или вещество сравнения налоксон 1 мг/кг внутривентрально) или физиологический раствор и помещали животное в установку на 10 мин. Затем производили угашение предпочтения места в течение 7 дней, которое заключалось в ежедневном его тестировании без введения алкоголя и иных препаратов. На 11-й день эксперимента регистрировали компульсивное поведение по закапыванию шариков после введения веществ. На 18-й день эксперимента производили введение этанола и регистрировали возобновление условной реакции предпочтения места. Части животных вводили агрелакс или налоксон за 5 мин до введения этанола для определения влияния на возобновление условной реакции предпочтения места. **Результаты.** После введения физиологического раствора в 8-й день эксперимента животные проводили в ассоциированной с введением этанола камере 71% времени. У крыс, получавших агрелакс или налоксон, наблюдали снижение времени пребывания в камере, ассоциированной с этанолом, до 45% ($p < 0,05$) и 39% ($p < 0,01$) соответственно. Налоксон вызывал блокаду возобновления предпочтения места введения этанола, что проявлялось уменьшением на 26% времени нахождения в предпочитаемой камере, ассоциированной с введением этанола. Антагонист рецепторов грелина агрелакс (10 мкг в 20 мкл, интраназально) не вызывал снижения воспроизведения условной реакции предпочтения места введения этанола. На 10-й день эксперимента после введения физиологического раствора животные закапывали $17,2 \pm 2,3$ шарика в marble-тесте. Агрелакс и налоксон снижали число закопанных шариков на фоне отмены этанола до $13 \pm 3,5$ ($p < 0,05$) и $11 \pm 2,4$ ($p < 0,05$) соответственно. **Заключение.** Агрелакс снижает проявление условной

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реакции предпочтения места введения этанола и компульсивное поведение крыс на фоне его отмены, что сравнимо с действием налоксона. В то же время в отличие от налоксона агрелакс не вызывает снижения возобновления предпочтения места введения этанола. Таким образом, показана важная роль системы грелина в механизмах подкрепляющего действия алкоголя и перспектива использования новых антагонистов грелина в коррекции патологического влечения.

Ключевые слова: грелин, агрелакс, условная реакция предпочтения места, алкоголь, компульсивность

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INTRODUCTION

Among the neuropeptides mediating the emotional effects of psychoactive substances [1], the peptide hormone ghrelin, discovered in the late XX century, has attracted considerable attention [2]. Ghrelin is produced in the gastric mucosa, consists of 28 amino acids, and exists in three isoforms: acylated ghrelin, unacylated (desacyl-ghrelin), and obestatin [3, 4]. The ghrelin receptor has two molecular forms; however, biological activity is attributed exclusively to the first form, GHSR1A. The ghrelin receptor is localized in the pancreas, adrenal glands, thyroid gland, myocardium, as well as in brain structures including the anterior pituitary, arcuate nucleus of the hypothalamus, hippocampus, substantia nigra, and ventral tegmental area [5]. Ghrelin has been shown to increase food intake via its action on the hypothalamus, which has led to its designation as a “hunger hormone” [6]. Furthermore, ghrelin stimulates appetite, thereby participating in the regulation of food motivation [7, 8].

In recent years, ghrelin has also been demonstrated to participate in the reinforcement mechanisms underlying the development of alcohol and drug dependence [7]. Thus, following ghrelin administration, ethanol intake in alcohol-experienced rats increased extracellular dopamine levels in the ventral tegmental area [9]. Food restriction, which elevates ghrelin levels [10], has also been shown to increase amphetamine- and cocaine-induced locomotor activity, enhance cocaine-seeking behavior, and elevate cocaine and amphetamine self-administration in rats [11]. Intracerebroventricular and intra-VTA administration of ghrelin increased alcohol consumption in mice [12, 13].

Ghrelin is involved in stress mechanisms, as corticotropin-releasing hormone (CRH) is considered one of the potential targets of ghrelin in the stress response. Ghrelin has been shown to activate CRH neurons in mice [14]. Extrahypothalamic targets directly affected by ghrelin include the extended amygdala circuitry — a stress-responsive brain system that mediates reinforcement and addiction mechanisms [15]. Ghrelin administration has been demonstrated to activate CRH neurons and, consequently, the hypothalamic-pituitary-adrenal (HPA) axis [16]. Activation of this axis is essential when ghrelin exerts a protective role against the development of depressive symptoms under chronic stress [17].

AIM

The aim of this study was to investigate the involvement of ghrelin and its receptor antagonist [D-Lys3]-GHRP-6 in the mechanisms of conditioned reinforcement in rats with long-term ethanol consumption.

MATERIALS AND METHODS

Animals. A total of 46 male Wistar rats obtained from the Rappolovo laboratory animal nursery (Leningrad Region) were used in the study. The animals were housed in standard plastic cages, 8–10 individuals per cage, with free access to food and water under an inverted light cycle from 8:00 to 20:00 at a temperature of 22 ± 2 °C. All experiments were conducted during the autumn–winter period.

Conditioned place preference test. To establish conditioned place preference (CPP) for ethanol administration in rats, a two-compartment apparatus with distinct floor textures (smooth vs. grid) was used. During CPP acquisition, animals were sequentially placed into two compartments separated by a partition for 30 min each, with a 2 h interval between sessions, over 8 consecutive days. During the 1 h interval between sessions, rats were kept in their home cages. Prior to placement into the first compartment, rats received an intraperitoneal injection of 0.9% sodium chloride solution (saline); prior to placement into the second compartment, animals were injected intraperitoneally with ethanol at a dose of 0.5 g/kg. The control group received saline intraperitoneally in the second compartment. To control for potential effects of floor texture on the acquisition of ethanol-induced CPP, experimental animals were divided into two subgroups. Rats in the first subgroup were initially placed into the compartment with a grid floor, and those in the second subgroup — into the compartment with a smooth floor. To assess the acquisition of ethanol-induced CPP, on day 9 of the experiment, the time spent in compartments with different floor textures was recorded over 15 min under conditions of free movement within the two-compartment apparatus. The data were expressed as the percentage of time spent in the ethanol-paired compartment relative to the total test duration. In subsequent experiments, only animals that spent more than 60% of the time



in the alcohol-paired compartment (chamber preference criterion) were used. Such animals constituted approximately half of all rats in which CPP acquisition was attempted. On day 9 of the experiment, these animals received a single intranasal administration of the ghrelin receptor antagonist Agrelax at a dose of 10 μ g in 20 μ L, or intraperitoneal naloxone at a dose of 1 mg/kg, without ethanol administration, to evaluate the effects of these substances on CPP expression. Control animals under the same experimental conditions received an equivalent dose of saline intranasally or intraperitoneally. Place preference extinction was then conducted over 7 days, which consisted of daily testing without ethanol or any drug administration. On day 11 of the experiment, compulsive behavior was assessed using the marble-burying test following drug administration. By day 7 of extinction, CPP was no longer observed, i.e., animals spent approximately equal time in both compartments. On day 18 of the experiment, ethanol was administered and reinstatement of conditioned place preference was assessed. Ethanol (0.5 g/kg) was administered intraperitoneally, the animal was placed into the apparatus for 10 min, and CPP reinstatement (spending more than 60% of time in the ethanol-paired compartment) was recorded. Some animals received Agrelax or naloxone 5 min prior to ethanol administration to determine their effects on the reinstatement of conditioned place preference. A subset of animals (9 rats) received a single additional intranasal administration of the ghrelin receptor antagonist Agrelax (10 μ g) 5 min prior to ethanol administration, another subset (10 rats) received intraperitoneal naloxone (1 mg/kg), and another subset (9 rats) received 20 μ L of saline, to assess their effects on CPP reinstatement.

Pharmacological substances. The ghrelin receptor antagonist Agrelax, synthesized at the Institute of Experimental Medicine, was used in the study. It was dissolved in distilled water at a concentration of 0.5 mg/mL and administered intranasally at a dose of 10 μ g in 20 μ L (10 μ L per nostril). Naloxone (Tocris, England) was dissolved in distilled water and administered intraperitoneally at a dose of 1 mg/kg. Control animals received an equivalent volume (20 μ L) of 0.9% sodium chloride solution.

Statistical significance was assessed using SPSS SigmaStat 3.0 and GraphPad Prism 6 software by one-way analysis of variance (ANOVA). One-way ANOVA

was used to compare the control and experimental groups. The nonparametric Kruskal–Wallis test was applied for group comparisons. Differences were considered statistically significant at $p < 0.05$. Data are presented as mean $\pm$ standard error of the mean (SEM).

RESULTS

A total of 52 rats from the same delivery were included in the experiment. Eight animals comprised the control group, which received 0.9% sodium chloride solution instead of ethanol during CPP acquisition. Animals with established ethanol-induced CPP were divided into three groups: 8 animals received intranasal administration of 20 μ L of 0.9% sodium chloride solution during testing, 8 animals received naloxone (1 mg/kg) as a reference drug, and 8 animals received intranasal administration of Agrelax solution at a dose of 20 μ g in 20 μ L. The data presented below are from animals used to assess the anti-alcohol effects of ghrelin peptides and the reference compound naloxone. Control animals receiving intranasal 20 μ L of saline spent $81.5 \pm 5.7\%$ of the total time in the CPP chamber ($p < 0.05$ vs. control). The opioid receptor antagonist naloxone reduced the time spent in the CPP chamber (to $55.8 \pm 6.9\%$ of the total time), while the ghrelin receptor antagonist Agrelax reduced the time spent in the CPP chamber (to $63.8 \pm 4.7\%$ of the total time) (Fig. 1). Thus, naloxone significantly affected

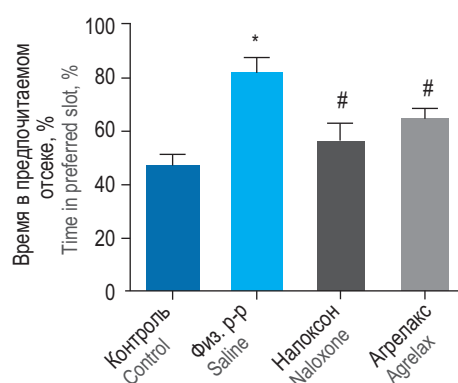


Fig. 1. Expression of conditioned place preference response (CPPR) of ethanol. * — $p < 0.05$ in relation to the control; # — $p < 0.05$ in relation to the group with the production of CPPR with ethanol (drawing by the authors)

Рис. 1. Экспрессия условной реакции предпочтения места (УРПМ) введения этанола. * — $p < 0,05$ по отношению к контролю; # — $p < 0,05$ по отношению к группе с выработкой УРПМ введения этанола (рисунок авторов)

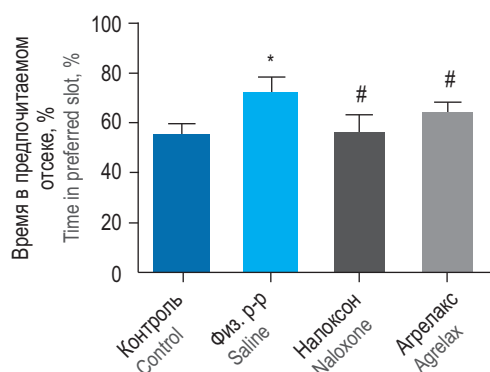


Fig. 2. Reinstatement conditioned place preference response (CPPR) with ethanol. * — $p < 0.05$ in relation to the control; # — $p < 0.05$ in relation to the group with the production of CPPR with ethanol (drawing by the authors)

Рис. 2. Возобновление условной реакции предпочтения места (УРПМ) введения этанола. * — $p < 0,05$ по отношению к контролю; # — $p < 0,05$ по отношению к группе с выработкой УРПМ введения этанола (рисунок авторов)

CPP expression, while the ghrelin antagonist Agrelax blocked the expression of the response, manifested as a decrease in the time spent in the preferred chamber associated with ethanol administration.

The ethanol CPP extinction test revealed that animals spent $55.1 \pm 4.2\%$ of the total time in the ethanol-paired chamber, indicating that CPP was not expressed and did not reach the 60% preference criterion. Following ethanol administration (priming), rats demonstrated reinstatement of CPP, spending on average $72.1 \pm 5.7\%$ of the total time in the alcohol-paired chamber ($p < 0.05$). The ghrelin receptor antagonist Agrelax ($10 \mu\text{g}$ in $20 \mu\text{L}$, intranasally) did not reduce the reinstatement of ethanol-induced CPP following ethanol challenge. Naloxone blocked the reinstatement of ethanol-induced place preference, manifested as a decrease in the time spent in the preferred ethanol-paired chamber to $52.9 \pm 11.2\%$ (Fig. 2).

In the marble-burying test on day 10 of the experiment, following saline administration, animals buried 16.6 ± 1.3 marbles. Naloxone and Agrelax reduced the number of marbles buried during ethanol withdrawal to 12.2 ± 1.2 ($p < 0.05$) and 12.7 ± 1.4 ($p < 0.05$), respectively (Fig. 3).

DISCUSSION

The present study demonstrated that intranasal administration of the peptide ghrelin antagonist Agre-

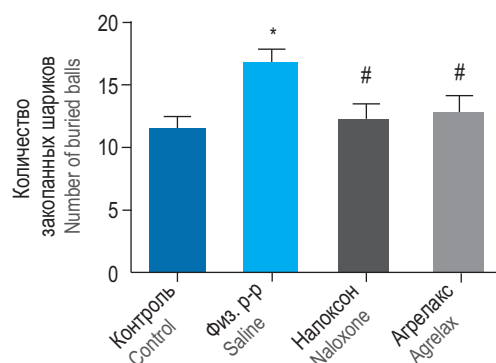


Fig. 3. Number of buried marbles in marble test after ethanol withdrawal. * — $p < 0.05$ in relation to the control; # — $p < 0.05$ in relation to the group with the production of CPPR with ethanol (drawing by the authors)

Рис. 3. Число закопанных шариков в marble-тесте на фоне отмены этанола. * — $p < 0,05$ по отношению к контролю; # — $p < 0,05$ по отношению к группе с выработкой условной реакции предпочтения места введения этанола (рисунок авторов)

lax delayed the acquisition of ethanol-induced CPP in rats. However, expression of ethanol-induced CPP following extinction was not reduced by Agrelax administration. A similar effect was previously shown by our group following administration of the ghrelin receptor antagonist [D Lys3]-GHRP-6 on ethanol-induced place preference in intact rats. However, unlike Agrelax, [D Lys3]-GHRP-6 reduced CPP expression and its reinstatement after extinction [17]. Agrelax reduced the expression of ethanol-induced conditioned place preference and compulsive behavior during ethanol withdrawal, an effect comparable to that of naloxone. However, unlike naloxone, Agrelax did not reduce the reinstatement of ethanol-induced place preference. These findings are generally consistent with the literature regarding the potential involvement of the ghrelin system in reinforcement mechanisms [18]. In particular, several studies have shown that the central ghrelin system is important for intracranial reinforcement processes activated by addictive substances [19,20]. For example, administration of the ghrelin receptor antagonist [D Lys3]-GHRP-6 significantly reduced the reinforcing properties of amphetamine as well as the psychomotor stimulant cocaine. Of interest are our previously reported data [17] demonstrating that intraperitoneal administration of ethanol at doses of 0.5, 0.75, and 1.5 g/kg may possess both reinforcing and aversive properties, and that the re-



inforcing effects do not always increase with increasing ethanol dose. Low doses of ethanol (0.5–0.75 g/kg) typically exhibit a clear reinforcing effect, in this case associated with the preferred CPP chamber. This appears to be related to individual differences among animals within the heterogeneous study population.

The present study demonstrates the involvement of the central ghrelin system in the mechanisms of pathological alcohol craving and the potential utility of ghrelin receptor antagonists for reducing reinforcement activated by this system. Studies on the ghrelin system reported in the scientific literature have primarily focused on the regulation of feeding behavior [21]. In particular, it has been shown that food restriction, which elevates ghrelin levels [22], also increases amphetamine- or cocaine-induced locomotor activity, enhances cocaine-seeking behavior, and elevates cocaine and amphetamine self-administration in rats [13].

Our findings are also consistent with other experiments using the ghrelin receptor antagonist [D Lys3]-GHRP-6, which is structurally a fragment of substance P, the main representative of the neurokinins involved in the regulation of alcohol and psychoactive substance consumption.

A significant reduction in the reinforcing properties of ethanol has been demonstrated, as measured by dopamine levels in the nucleus accumbens and behavioral parameters (locomotor activity and conditioned place preference). The study of the physiological role of ghrelin and its receptors in the mechanisms of reinforcement and dependence on psychoactive substances, as well as the effects of ghrelin ligands on emotional, exploratory, and motor activity during alcohol exposure and stress, represents a relevant problem for both physiology and neuropharmacology. Indeed, the ghrelin system is increasingly considered a target for pharmacological intervention [13]. However, no studies have been conducted to date examining the regulation of emotional, exploratory, and motor activity during chronic alcohol exposure by ghrelin or components of its system (desacyl-ghrelin, obestatin).

In contrast, intracerebroventricular or local administration of ghrelin into the ventral tegmental area increased alcohol consumption in mice [13]. Furthermore, the effect of ghrelin was shown to be most pronounced in rodents with prior alcohol experience, as peripheral ghrelin administration to alcohol-naïve

rats only marginally increased alcohol intake [13,23]. Thus, ghrelin and its GHSR1A receptors may regulate the level of consumption and seeking of addictive substances. This suggests that treatment of patients with alcohol dependence using pharmacological agents targeting the ghrelin system may represent a promising direction in modern psychopharmacology and biological addiction medicine.

CONCLUSION

Thus, the novel ghrelin receptor antagonist Agrelax reduced the expression of ethanol-induced conditioned place preference and compulsive behavior in rats during ethanol withdrawal, an effect comparable to that of naloxone. However, unlike naloxone, Agrelax did not reduce the reinstatement of ethanol-induced place preference. This study demonstrates the important role of the ghrelin system in the mechanisms underlying the reinforcing effects of alcohol and the potential of novel ghrelin receptor antagonists for the correction of pathological craving.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Experiments with animals were carried out in accordance with international rules (Directive 2010/63/EU of the European Parliament and of the Council of the European Union of September 22, 2010 on the protection of animals used for scientific purposes).

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.



Эксперименты с животными проводили в соответствии с международными правилами (Директивой 2010/63/EU Европейского парламента и

Совета Европейского союза от 22 сентября 2010 года по охране животных, используемых в научных целях).

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Metformin as an adjuvant therapeutic agent in central nervous system disorders

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ABSTRACT. The article reviews current evidence on the neuroprotective properties of metformin in central nervous system disorders, focusing on its mechanisms of action mediated by 5'AMP-activated protein kinase (AMPK) activation, which regulates energy metabolism, autophagy, neuroinflammation, and oxidative stress. Preclinical studies demonstrate reduced α -synuclein pathology in Parkinson's disease, decreased β -amyloid accumulation in Alzheimer's disease, and immunomodulatory effects in multiple sclerosis. Clinical data reveal conflicting evidence: some studies report improvements in cognitive/motor functions, while others show no significant benefits. The authors emphasize the necessity of large-scale randomized trials to evaluate metformin's efficacy as an adjuvant therapy, given dose-dependent effects, treatment duration variability, and population-specific responses.

Keywords: metformin, cognitive impairment, Parkinson's disease, Alzheimer's disease, multiple sclerosis

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Метформин как препарат для адъювантной терапии заболеваний центральной нервной системы

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РЕЗЮМЕ. В статье обобщены современные данные о нейропротекторных свойствах метформина при заболеваниях центральной нервной системы. Основное внимание уделено механизмам действия через активацию 5'АМФ-активируемой протеинкиназы (АМРК), модулирующей энергетический метаболизм, аутофагию, нейровоспаление и окислительный стресс. Рассмотрены доклинические исследования, демонстрирующие снижение патологии α-синуклеина при болезни Паркинсона, уменьшение накопления β-амилоида при болезни Альцгеймера и иммуномодуляцию при рассеянном склерозе. Клинические данные демонстрируют противоречивые результаты — часть работ указывает на улучшение когнитивных/двигательных функций, другие не подтверждают значимых эффектов. Подчеркивается необходимость масштабных рандомизированных исследований для оценки роли метформина как адъювантной терапии, учитывая зависимость эффектов от дозы, длительности лечения и популяционных особенностей.

Ключевые слова: метформин, когнитивные нарушения, болезнь Паркинсона, болезнь Альцгеймера, рассеянный склероз

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INTRODUCTION

Metformin is a biguanide that has become one of the most commonly used hypoglycemic agents due to its affordability, high safety profile, and effectiveness. The mechanisms of metformin's antidiabetic action are primarily associated with the inhibition of gluconeogenesis in the liver, increased glucose utilization by muscles, increased tissue sensitivity to insulin, and reduced insulin inactivation [1, 2]. A new wave of interest in the drug has been sparked by recent data showing that metformin crosses the blood-brain barrier (BBB) and can therefore directly affect cells in the central nervous system (CNS) [3, 4]. This hypothesis is confirmed by the results of a number of studies on animal models of various diseases of the nervous system, including multiple sclerosis, Alzheimer's disease, Parkinson's disease, epilepsy, stroke, etc. [5–8].

AIM

The aim of this review is to summarize the results of studies on the mechanism of action and efficacy of metformin in the treatment of CNS diseases.

METFORMIN AND PARKINSON'S DISEASE

Parkinson's disease (PD) is a progressive neurodegenerative disorder that develops as a result of the death of dopaminergic neurons in the substantia nigra and striatum and is characterized by the development of rigidity, bradykinesia, resting tremor, postural instability, and a wide range of non-motor symptoms [9, 10]. PD remains an incurable disease; all currently available therapeutic approaches are aimed at symptomatic correction and do not prevent the progression of the disease, which is why the search for new treatments that alter the course of the disease is one of the main tasks. Current data confirm a direct link between type 2 diabetes mellitus (T2DM) and an increased likelihood of developing PD, suggesting common molecular mechanisms underlying these diseases [11–13]. In this regard, metformin has been proposed as a promising drug for the treatment of PD. Studies in animal models of PD have shown that the neuroprotective effect of metformin is achieved

through a complex effect on energy metabolism, oxidative stress, inflammation, and autophagy. The most studied mechanisms of metformin's action are mediated by the activation of 5'AMP-activated protein kinase (AMPK), which is an ubiquitously expressed kinase that is considered a “sensor” of cellular metabolic status. AMPK has been shown to coordinate key cellular processes such as autophagy, cell growth, and mitochondrial quality control [14]. In a study using a PD model (administration of rotenone to rats), it was shown that an 18-day course of metformin activates the AMPK-FOXO3 pathway (transcription factor) pathway, reduces vascular endothelial growth factor production, caspase-3/9 activation, and cytoplasmic cytochrome C levels [15]. Young-Kyoung Ryu et al. (2020) studied the effect of metformin on motor function in a mouse model of PD induced by 6-hydroxydopamine (6-OHDA). The authors showed that oral administration of metformin at a dose of 100–200 mg/kg for 4 weeks activates AMPK signaling pathways, stimulates the production of the neurotrophic factor BDNF, suppresses microglial activation, and significantly improves motor function in mice with 6-OHDA-induced PD [16]. In another study investigating the neuroprotective potential and main mechanisms of action of metformin in a rotenone-induced mouse model of PD, it was shown that 10 days of metformin administration (300 mg/kg per day, intraperitoneally) attenuated the loss of dopaminergic neurons by suppressing lipid peroxidation and significantly reduced the rotenone-induced increase in cleaved caspase-3 and α -synuclein accumulation in the substantia nigra [17]. N. Katila et al. (2017) also demonstrated that metformin administration led to a decrease in the level of serine 129 phosphorylated α -synuclein (α -synuclein pSer129) through the activation of protein phosphatase 2A (PP2A), which is known to mediate the dephosphorylation of α -synuclein. According to the authors, the activation of PP2A by metformin can occur through both AMPK-dependent and AMPK-independent pathways [18]. Similar results were obtained when metformin (at a dose of 200 mg/kg per day) was administered to mice in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD: a significant decrease in α -synuclein pSer129 levels was observed, due to PP2A activation. In this study, the metformin-mediated decrease in pathological



α -synuclein levels, together with autophagy activation, increased production of neurotrophic factors (BDNF, GDNF), and regulation of downstream signaling pathways (Akt, Erk1/2) contributed to the restoration of dopamine content in the striatum and improvement of motor functions in mice [19]. In addition, metformin attenuates lipopolysaccharide (LPS)-induced neuroinflammation, which may be due to the drug's inhibitory effect on the translocation of the transcription factor NF- κ B (nuclear factor kappa B) to the nucleus and suppression of proinflammatory cytokine production in various cell types [20, 21]. This is an important fact, since there is a model of PD in which a number of links in the pathogenesis of PD are modeled by administering high doses of LPS to laboratory animals [22]. However, despite the impressive number of studies demonstrating the positive effects of metformin in PD, there are studies showing the opposite results. For example, a 2016 study showed that metformin exacerbated damage to dopaminergic neurons in mice with an MFTP model of PD [23]. The clinical data currently available on the effect of metformin on the course of PD are also ambiguous. According to a study by M.L. Wahlqvist et al. (2012), patients with T2DM had a twofold increase in the risk of developing PD, which decreased to 1.3 with the use of hypoglycemic drugs; the confidence interval (CI) for the odds ratio (OR) was 0.77–2.19. However, the use of metformin as monotherapy did not reduce the risk of developing PD, while the combined use of metformin and sulfonylurea reduced the risk of developing PD to 0.78 (0.61–1.01) [13]. A 2019 US analysis of a 5-year follow-up of 5,528 patients with T2DM (mean age 63.2 $\pm$ 10.9 years) showed that long-term metformin therapy (more than 4 years) significantly reduced the risk of developing PD among patients with T2DM (OR 0.19; 95% CI 0.12–0.31) [24]. Conversely, according to a systematic review published in 2020, which analyzed 19 studies involving more than 250,000 people, no positive effects associated with the use of metformin for the treatment of PD were identified. Moreover, the review showed that metformin use may even increase the risk of developing PD [25]. At the same time, a meta-analysis published in 2023 covering 15 studies involving a total of 2,910,405 patients with T2DM found no significant association between hypoglycemic drugs, including

metformin, sulfonylureas, glucagon-like peptide-1 (GLP-1) receptor agonists, and glitazones with the risk of developing PD [26].

It is noteworthy that a recent randomized, double-blind, placebo-controlled clinical trial showed that exenatide, a GLP-1 receptor agonist, improves motor function in patients with PD [27]. These data suggest that increasing GLP-1 with metformin may be another potential molecular mechanism contributing to its neuroprotective effect in PD [28]. Furthermore, it is interesting to note that metformin does not affect the pharmacotherapeutic effects of levodopa, suggesting that the combination of both drugs may be useful in the treatment of levodopa-induced dyskinesias in PD without compromising the efficacy of levodopa [29]. These data support the need for further study of metformin as a drug that potentiates the action of antiparkinsonian agents.

METFORMIN AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a neurodegenerative disease characterized by a gradual, subtle onset in presenile or senile age, steady progression of memory and higher brain function disorders leading to dementia with the formation of a characteristic complex of neuropathological, neuroimaging, and biochemical features. The main histopathological feature of AD is the deposition of β -amyloid (A β) in the brain parenchyma and in the walls of blood vessels (with the formation of senile plaques), which has neurotoxic properties, leading to damage and death of neurons. There is ample evidence that the molecular mechanisms of T2DM and AD have points of contact, and one of the common features linking the two diseases is insulin resistance. In particular, it has been shown that insulin resistance in brain cells (especially in the hippocampus and cortex) is associated with the accumulation of A β and tau pathology [30]. Insulin signaling in the brain, which is crucial for neuronal function, involves the activation of insulin receptors (IR) and IGF-1R, leading to the phosphorylation of IRS protein and subsequent activation of PI3K/ Akt and MAPK pathways, which regulates glucose metabolism, synaptic plasticity, and cell survival. In insulin resistance, this cascade is disrupted due to increased phosphorylation of serine/threonine in IRS proteins, decreased tyrosine phosphorylation, and reduced activation of this path-



way [31, 32]. In this regard, one of the main areas of research into the mechanisms of metformin action in AD is the analysis of its effect on insulin resistance and insulin signaling in the brain.

Metformin has been shown to increase insulin sensitivity in the CNS by activating AMPK and enhancing the insulin/IGF-1 signaling pathway [33]. In a study by K.A. DiTacchio (2015) on transgenic A β PP mice showed that administration of metformin (at a dose of 350 mg/kg per day) for 14–16 months increases insulin sensitivity in males, increases lifespan, and slows down the degradation of the estrous cycle in females [34]. Metformin also improved cognitive function in APP/PS1 transgenic mice (an animal model of AD) and contributed to a reduction in the deposition of pathological A β and tau proteins in the hippocampus and cerebral cortex [35]. S.A. Farr et al. showed that metformin reduces the expression of APPc99 and p-tau proteins in SAMP8 mice (animals characterized by accelerated aging; they spontaneously develop signs of aging as early as 6–8 months instead of 18–24 months in normal mice, making them a convenient model for research). Thus, the use of metformin in SAMP8 mice significantly reduced the hyperphosphorylation of tau and APPc99 proteins, which led to improved learning and memory processes [36].

The mechanisms by which metformin reduces the accumulation of A β and tau protein are associated with the activation of AMPK, which in turn activates MARK1 kinase, which regulates the processing of amyloid precursor protein (APP). In addition, AMPK enhances autophagy by inhibiting mTOR, promoting A β clearance [37]. However, in some studies, long-term use of metformin increased A β levels due to the suppression of insulin degradase (IDE), which is involved in the destruction of A β [38].

Another mechanism of metformin's neuroprotective action in AD is mediated by its anti-inflammatory effects. It is known that in AD, as in PD, activated microglia intensify the process of neuroinflammation by secreting pro-inflammatory cytokines. Metformin inhibits NF- κ B activation via AMPK, reducing cytokine production. Thus, in rodent models, metformin reduced microglial activation and astrogliosis, improving neuronal survival [37]. In addition, metformin has been shown to activate AMPK/PGC-1 α -dependent mitochondrial biogenesis, increasing energy meta-

bolism [39]. However, at high doses, metformin can inhibit complex I of the respiratory chain, increasing oxidative stress (a paradoxical effect) [40].

In addition to preclinical studies, there are currently many studies demonstrating the effectiveness of metformin in clinical practice for AD. A study by Tseng Chin-Hsiao (2019) showed that metformin stops or slows the onset of dementia in adult patients with T2DM [41]. From 2008 to 2012, Columbia University (New York) conducted a pilot study of 80 patients with amnesic mild cognitive impairment. The participants were overweight, but none of them had diabetes. Patients received either metformin at a daily dose of 2000 mg or a placebo for one year. Cognitive function was assessed using the Systemic Reasoning Test (SRT) and the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog). Secondary endpoints were glucose uptake by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) in the posterior cingulate cortex and plasma levels of A β 42, the most toxic form of the A β peptide. The metformin group showed slightly higher SRT scores than the placebo group (9.7 ± 8.5 vs. 5.3 ± 8.5 ; $p=0.02$). No differences in ADAS-Cog scores, glucose uptake, or plasma A β 42 levels were found between the groups [42]. A.M. Koenig et al. (2017) conducted a similar study, but in addition to assessing cognitive function and neuroimaging in patients, they measured the concentration of metformin in cerebrospinal fluid (CSF). The results of the study showed that metformin use improves executive function, learning, and attention. The researchers also noted that metformin was safe, well tolerated, and measurable in CSF at a mean steady-state concentration of 95.6 ng/mL [43]. An interesting study was conducted based on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI¹) in 2022. In addition to cognitive functions, the assessment included levels of A β , tau, and phosphorylated tau in CSF, as well as neuroimaging data (hippocampal volume and cortical thickness were assessed). It turned out that patients with T2DM who received metformin treatment in the early stages of AD had better cognitive performance and lower levels of tau and phosphorylated tau in the CSF than patients who did not receive metformin. Patients receiving metformin also had less severe atrophy in the hippocampus and

¹ Available at: <https://adni.loni.usc.edu/> (accessed: 10.09.2025).



cortex according to neuroimaging data [44]. However, despite numerous studies demonstrating the positive effects of metformin on cognitive function, there are studies that cast doubt on the available results. Thus, a recent meta-analysis found no significant association between metformin use and the risk of developing AD (OR 1.17; 95% CI 0.88–1.56; $p=0.291$). Moreover, subgroup analysis showed that among Asians, the risk of developing AD was significantly higher in patients taking metformin than in those who did not take it (OR 1.71; 95% CI 1.24–2.37; $p=0.001$) [45].

A randomized controlled trial (MET-FINGER, phase IIb) is currently underway to evaluate a new multimodal approach to the prevention of cognitive impairment and disability, combining lifestyle modification (diet, physical activity, cognitive training, monitoring of cardiovascular/metabolic risk factors, social interaction) with metformin in older adults at increased risk of dementia who do not have diabetes. The study is expected to provide decisive evidence for the implementation of innovative combined strategies for the prevention of AD [46].

Since 2021, a multicenter randomized controlled trial of metformin in the prevention of dementia in AB, phase 2/3 (MAP), has been underway. This study involves 326 people aged 55 to 90 who are overweight or obese, without diabetes, and with early or late mild cognitive impairment. Study participants receive 2000 mg of extended-release metformin per day or placebo (1:1). In addition to neuropsychological testing, the study assesses changes in hippocampal volume and white matter hyperintensity in the brain based on neuroimaging data, changes in the standardized uptake value ratio (SUVR) A β , changes in SUVR tau in the medial and inferior lateral temporal cortex, as well as changes in plasma AD biomarkers. The study is expected to continue until 2027 [47].

Thus, metformin demonstrates the potential to modulate key mechanisms of AD (A β and tau pathology, neuroinflammation, insulin resistance), but its effects depend on dose, age, duration of use, and time of initiation of therapy. Further preclinical studies are needed to optimize treatment regimens and clarify risks.

METFORMIN AND MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic demyelinating disease characterized by a complex of autoimmune

inflammatory and neurodegenerative processes leading to multiple focal and diffuse lesions of the central nervous system, resulting in disability and a significant reduction in quality of life.

The role of the immune system and neuroinflammation in the development of this disease is now beyond doubt and is confirmed by the high efficacy of modern immunomodulatory drugs used to treat MS. However, despite the effectiveness of the drugs used, the disease steadily progresses, transitioning to a secondary progressive form that develops as a result of the inevitable degeneration of neurons, which requires the search for new pharmacological agents that affect not only the inflammatory but also the neurodegenerative process in MS. Metformin has become a promising candidate for the treatment of MS due to its diverse mechanisms of action and well-established safety profile. Recent studies have shown that metformin affects key immunopathological mechanisms underlying the development of systemic autoimmune diseases, such as the balance between T helper 17 (Th17) and regulatory T lymphocytes (Tregs), autoantibody production, macrophage polarization, and cytokine synthesis [48]. Thus, W. Duan et al. (2019) showed that metformin, through AMPK activation, suppresses T-cell proliferation and Th17 cell differentiation, while promoting Treg development *in vitro*. The authors demonstrated that administration of metformin to NOD mice (mice with spontaneously developing type 1 autoimmune diabetes) at a dose of 200 mg/kg alleviates the course of autoimmune insulin syndrome and significantly reduces the amount of interferon- γ (IFN- γ) and CD4 (+) interleukin-17 (IL-17) (+) T cells [49]. N. Nath et al. (2010) showed that metformin (20–100 mg/kg) successfully slowed disease progression, reduced immune cell infiltration, and decreased the expression of proinflammatory cytokines (IFN- γ , TNF α , IL-1 β , IL-6, and IL-17) and proinflammatory mediators such as matrix metalloproteinase 9 (MMP-9) and chemokine RANTES/CCL5 in the CNS of animals with experimental autoimmune encephalitis (EAE). The authors demonstrated that metformin activated AMPK in macrophages, thereby inhibiting the biosynthesis of phospholipids and neutral lipids, as well as suppressing the expression of proinflammatory cytokines induced by endotoxin (LPS) and their mediators (iNOS and cyclooxygenase) [50].



The effects of metformin on B cells include modulation of activation and differentiation processes, reduction of antibody production, and influence on B cell-mediated inflammation, which plays a key role in the pathogenesis of MS [51]. The effect of metformin on the mTOR pathway contributes to a reduction in the proliferation of inflammatory cells and regulated differentiation of immune cells. In addition, this modulation affects myelin regeneration processes and neuronal survival mechanisms. In a recent study, N. Sanadgol et al. (2020) showed that metformin (50 mg/kg body weight per day) induces remyelination in mice with cuprizone-induced demyelination through direct activation of AMPK and indirect regulation of the AMPK/Nrf2/mTOR pathway in oligodendrocytes. Metformin also reduced brain apoptosis markers (cleaved caspase-3/ α -tubulin and Bax/Bcl-2 ratios) and improved motor activity in mice in the Open Field test [52]. Another study investigated the effect of metformin on remyelination in the “acute” and “delayed” periods of EAE. Metformin contributed to a reduction in demyelination and improvement in motor function in mice with EAE in the “acute” period, but did not show its effectiveness in the “delayed” period [53].

Unlike the many promising fundamental studies of metformin's effects on animal models of MS-EAE, the number of studies investigating the effects of metformin on patients with MS is limited. A cohort study conducted by L. Negrotto et al. on MS patients receiving metformin (850–1500 mg/day) demonstrated a significant reduction in the total number of new T2 lesions and contrast-enhancing lesions in the brain and spinal cord according to neuroimaging data. The effect was observed after 6 months of therapy and persisted for up to 24 months. In addition, the study showed increased AMPK expression, decreased IFN- γ and IL-17 production, and an increased percentage of Tregs in MS patients receiving metformin [54]. In 2024, the results of a prospective, open-label, randomized controlled trial were published, which aimed to study the efficacy and safety of metformin as an adjuvant therapy to interferon beta 1a (IFN β -1a) in patients with relapsing-remitting multiple sclerosis (RRMS). Patients were assessed for IL-17, IL-22, malondialdehyde (MDA), T2 lesions on magnetic resonance imaging (MRI), and expanded disability status scale

(EDSS) at baseline and after 6 months. The study showed that adding metformin to IFN β -1a contributed to a decrease in the oxidative stress marker malondialdehyde, but no statistically significant effect on immunological, neuroimaging, and clinical parameters was found [55].

Several clinical trials (Phase I and IIa) are currently underway to study the efficacy of metformin in MS. These studies are investigating the effect of metformin on remyelination processes, modulation of immune responses, and the impact on neurodegeneration in various subtypes of MS. The results of the studies have not yet been published, which does not allow conclusions to be drawn about the success of the clinical trials.

Thus, the available data support the efficacy of metformin in MS, but larger clinical trials are needed to definitively establish the therapeutic value of metformin, particularly its potential to improve existing MS treatments and provide a neuroprotective effect.

CONCLUSION

In neurology, drug repurposing programs include the search for drugs with neuroprotective activity or those that potentiate the action of neuroprotectors among known and widely used drugs. The basis for searching for neuroprotective properties in drugs intended for other purposes is the fact that signaling pathways in cells are characterized by a large number of cross-interactions, and some of them may be involved in the process of stimulating/intensifying neuron survival. Finding such intersections is possible thanks to advances in genomics, proteomics, bioinformatics, and the emergence of powerful analytical systems. Analysis of the current literature has shown that hypoglycemic agents, in particular metformin, have high neuroprotective potential. Currently, the preventive and therapeutic significance of metformin in diseases of the nervous system has been widely studied. According to the literature, metformin can modify the process of autophagy, prevent mitochondrial dysfunction, reduce neuroinflammation, and have a neuroprotective effect. However, there are studies that have not identified the neuroprotective effects of metformin. This may be due to differences in animal models and varying



Table 1

Effects of metformin in diseases of the central nervous system (compiled by the authors)

Таблица 1

Эффекты метформина при заболеваниях центральной нервной системы (составлено авторами)

Заболевание Disease	Животная модель или клинические испытания Animal model or clinical trials	Доза препарата / способ введения Dosage of the drug / route of administration	Механизмы, эффекты Mechanisms, effects	Ссылки на литературу References to literature
Болезнь Паркинсона Parkinson's disease	Мыши, МФТП-модель Mice, MPTP model	200 мг/кг, внутрибрюшинно 200 mg/kg, intraperitoneally	• улучшение двигательных функций; • improvement of motor functions; • повышение уровня дофамина в полосатом теле; • increased dopamine levels in the striatum; • снижение каспазы-3 и ингибирование апоптоза; • decreased levels of caspase-3 and inhibition of apoptosis; • снижение активации астроглии; • attenuation of astroglial activation; • активация AMPK и ингибирование mTOR; • AMPK activation and mTOR inhibition; • активация PP2A и снижение α-син pSer129; • activation of PP2A and reduction of pS129-α-syn; • повышение уровня нейротрофических факторов (BDNF, GDNF) и активация нисходящих сигнальных путей (Akt, Erk1/2); • increased levels of neurotrophic factors (BDNF, GDNF) and activation of downstream signaling pathways (Akt, Erk1/2)	[19]
	Мыши, ротеноновая модель Mice, rotenone model	300 мг/кг, внутрибрюшинно 300 mg/kg, intraperitoneally	• предотвращение дегенерации дофаминергических нейронов в черной субстанции; • prevention of degeneration of dopaminergic neurons in the substantia nigra; • снижение апоптоза, опосредованного каспазой-3; • attenuation of caspase-3-mediated apoptosis; • снижение накопления α-синуклеина; • decreased α-synuclein accumulation; • снижение уровня продуктов перекисного окисления липидов (4-HNE, MDA); • decreased levels of lipid peroxidation products (4-HNE, MDA)	[17]
	Мыши, модель 6-гидроксидотамина (6-OHDA) Mice, 6-hydroxydo- tamine (6-OHDA) model	100–200 мг/кг, перорально 100–200 mg/kg, orally	• улучшение двигательных функций; • improvement of motor functions; • активация сигнальных путей AMPK, стимуляция продукции нейротрофического фактора BDNF; • activation of AMPK signaling pathway, stimulation of BDNF production; • подавление активации микроглии; • suppression of microglial activation	[16]
	Крысы, ЛПС- индуцированная модель Rats, LPS-induced model	150 мг/кг 2 раза в день, перорально 150 mg/kg 2 times a day, orally	• уменьшение количества активированных микроглиальных клеток; • decreased number of activated microglial cells; • снижение уровня провоспалительных цитокинов (ФНО, ИЛ-1β, ИЛ-6) и микроглиальных провоспалительных фенотипов; • decreased levels of proinflammatory cytokines (TNF, IL-1β, IL-6) and microglial proinflammatory phenotypes; • снижение выработки активных форм кислорода; • decreased production of reactive oxygen species	[56]



Continuation of the Table 1 / Продолжение табл. 1

Заболевание Disease	Животная модель или клинические испытания Animal model or clinical trials	Доза препарата / способ введения Dosage of the drug / route of administration	Механизмы, эффекты Mechanisms, effects	Ссылки на литературу References to literature
Болезнь Альцгеймера Alzheimer's disease	Трансгенные мыши A β PP A β PP transgenic mice	350 мг/кг, перорально 350 mg/kg, orally	- повышение чувствительности к инсулину у самцов; - increased insulin sensitivity in males; - увеличение продолжительности жизни у самок; - extended lifespan in females	[34]
	Мыши SAMP8 SAMP8 mice	20–200 мг/кг, подкожно 20–200 mg/kg, subcutaneously	- улучшение обучения и памяти; - improvement of learning and memory; - снижение гиперфосфорилирования белков tau и APPc99; - reduction of hyperphosphorylation of tau and APPc99 proteins	[36]
	Крысы, скополамин- индуцированные когнитивные нарушения Rats, scopolamine- induced cognitive impairment	50, 100–200 мг/кг, через зонд 50, 100–200 mg/kg, via tube	- улучшение обучения и памяти; - improvement of learning and memory; - повышение уровня фосфорилированной AMPK; - increased levels of phosphorylated AMPK; - снижение уровня малонового диальдегида (MDA); - decreased levels of malondialdehyde (MDA); - повышение активности супероксиддисмутазы (SOD) в гиппокампе; - increased superoxide dismutase (SOD) activity in the hippocampus	[39]
	Трансгенные мыши APP/PS1 APP/PS1 transgenic mice	4 мг/мл в питьевой воде 4 mg/ml in drinking water	- способствование фагоцитозу белков Aβ и tau за счет усиления способности микроглиальной аутофагии - promotion of the phagocytosis of Aβ and tau proteins due to enhanced microglial autophagy capability	[35]
	Клинические данные Clinical data	2000 мг/день 2000 mg/day	- снижение риска развития деменции у пациентов с сахарным диабетом 2-го типа; - reduced risk of developing dementia in patients with type 2 diabetes mellitus; - улучшение результатов селективного теста на память у пациентов с легкими когнитивными нарушениями без диабета; - improved selective reminding test performance in patients with mild cognitive impairment without diabetes; - снижение уровней tau и фосфорилированного tau в СМЖ; - decreased levels of tau and phosphorylated tau in CSF	[42–44]
Рассеянный склероз Multiple sclerosis	Мыши C57BL/6 и SJL, экспериментальный аутоиммунный энцефаломиелит C57BL/6 and SJL mice, experimental autoimmune encephalomyelitis	20–100 мг/кг, через зонд 20–100 mg/kg, via tube	- замедление прогрессирования заболевания; - attenuation of the disease progression; - ограничение инфильтрации мононуклеарных клеток в ЦНС; - restriction of mononuclear cell infiltration into the central nervous system; - снижение экспрессии провоспалительных цитокинов (ИЛ-1β, ИЛ-6, ИЛ-17, ИФН-γ и ФНО-α) в ЦНС; - down-regulation of the expression of proinflammatory cytokines (IL-1β, IL-6, IL-17, IFN-γ and TNF-α) in the central nervous system; - подавление экспрессии матриксной металлопротеиназы 9 и хемокина (RANTES); - suppression of matrix metalloproteinase 9 and chemokine (RANTES) expression	[50]



Ending of the Table 1 / Окончание табл. 1

Заболевание Disease	Животная модель или клинические испытания Animal model or clinical trials	Доза препарата / способ введения Dosage of the drug / route of administration	Механизмы, эффекты Mechanisms, effects	Ссылки на литературу References to literature
	Мыши C57BL/6, экспериментальный аутоиммунный энцефаломиелит C57BL/6 mice, experimental autoimmune encephalomyelitis	100 мг/кг, через зонд 100 mg/kg, via tube	• снижение уровня Th17 и способствование пролиферации Tregs; • decreased Th17 levels and promotion of Tregs proliferation; • повышение уровней противовоспалительных цитокинов, трансформирующего фактора роста-β (TGF-β) и ИЛ-10; • increased levels of anti-inflammatory cytokines, transforming growth factor-β (TGF-β) and IL-10; • подавление активации пути мишени рапамицина у млекопитающих (mTOR); • suppression of activation of the mammalian target of rapamycin (mTOR) pathway	[48]
	Крысы, экспериментальный аутоиммунный энцефаломиелит Rats, experimental autoimmune encephalomyelitis	150 мг/кг, через зонд 150 mg/kg, via tube	• ослабление клинических симптомов; • alleviation of clinical symptoms; • повышение уровней Tregs и снижение уровней Th1 и Th17 в периферической нервной системе (ПНС) и ЦНС; • increased levels of Tregs and decreased levels of Th1 and Th17 in the peripheral nervous system (PNS) and CNS; • снижение демиелинизации и потери аксонов; • attenuation of demyelination and axonal loss; • ослабление воспалительных реакций и повышение экспрессии нейротрофических факторов, посредством активации AMPK; • attenuation of inflammatory responses and increased expression of neurotrophic factors via AMPK activation; • подавление окислительного стресса; • suppression of oxidative stress	[57, 58]
	Пациенты с ремиттирующим РС, когортное исследование Patients with relapsing-remitting MS, cohort study	850–1500 мг/день 850–1500 mg/day	• снижение общего количества новых T2-очагов и очагов, накапливающих контраст, в головном и спинном мозге; • decrease in the total number of new T2 lesions and contrast-enhancing lesions in the brain and spinal cord; • повышение экспрессии мРНК AMPK; • increased AMPK mRNA expression; • снижение выработки ИФН-γ и ИЛ-17 и повышение процента Tregs; • decreased production of IFN-γ and IL-17 and an increase in the percentage of Tregs	[54]
	Пациенты с ремиттирующим РС, клиническое исследование Patients with relapsing-remitting MS, clinical trial	2000 мг/день 2000 mg/day	• снижение уровня малонового диальдегида (MDA) • decreased levels of malondialdehyde (MDA)	[55]



doses of the drug. Clinical studies of metformin in the treatment of nervous system diseases are progressing slowly, with most of them being prospective or retrospective clinical studies; there is still a lack of large multicenter randomized controlled trials. The data are summarized in Table 1.

Thus, this literature review confirms that metformin can be considered a potential drug for the prevention and treatment of CNS diseases, but large-scale randomized controlled clinical trials are needed to provide more adequate clinical evidence.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, ac-

quisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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Foot examination methods: traditional and digital technologies (literature review)

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ABSTRACT. Diagnosis of foot conditions requires integration of traditional and digital methods to ensure a comprehensive assessment of anatomical and functional parameters. Classical techniques (clinical examination, morphometry, plantography, radiography) remain relevant for initial evaluation but are limited by subjectivity and static nature. Digital technologies — computerized plantography, weight-bearing computed tomography (WBCT) and 3D scanning — provide high accuracy, objectivity, and the capacity for dynamic assessment. Their combination enhances diagnostic precision, reveals biomechanical dysfunctions, supports the design of personalized orthotic devices, and enables the creation of standardized databases. Literature analysis confirms that synergistic integration of methods, supplemented by ultrasound and magnetic resonance imaging for tissue assessment, represents the optimal diagnostic strategy. The incorporation of digital technologies with artificial intelligence tools opens new prospects for deformation prediction and treatment personalization.

Keywords: foot, podiatry, plantography, radiography, computerized plantography, 3D scanning, morphometry

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Методы исследования стопы: традиционные и цифровые технологии (обзор литературы)

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РЕЗЮМЕ. Диагностика состояния стопы требует интеграции традиционных и цифровых методов, обеспечивающих комплексную оценку анатомо-функционального состояния. Классические подходы (клинический осмотр, морфометрия, плантография, рентгенография) сохраняют значение для первичной диагностики, однако их точность ограничена субъективностью и статичностью. Цифровые технологии — компьютерная плантография, нагрузочная компьютерная томография (weight-bearing computed tomography, WBCT) и 3D-сканирование — обеспечивают высокую точность, объективность и возможность динамического анализа. Их сочетание повышает диагностическую информативность, позволяет выявлять нарушения биомеханики, проектировать индивидуальные ортопедические изделия и формировать стандартизированные базы данных. Анализ литературы подтверждает, что синергия методов, дополненная ультразвуковыми исследованиями и магнитно-резонансной томографией для оценки мягких тканей, является оптимальной стратегией диагностики. Интеграция цифровых технологий с инструментами искусственного интеллекта открывает перспективы прогнозирования деформаций и персонализации лечения.

Ключевые слова: стопа, подиатрия, плантография, рентгенография, компьютерная плантография, 3D-сканирование, морфометрия

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The study of the morphofunctional characteristics of the foot, both normal and pathological, remains one of the key tasks of modern medicine [1]. Podiatry, which specializes in congenital, acquired, and post-traumatic changes in the foot and ankle joint, covers a wide range of clinical issues — from prevention and selection of orthopedic footwear to the development of surgical treatment algorithms [2]. Despite the variety of existing methods (visual examination, podometry, plantography, radiography, etc.), none of them can provide a comprehensive picture of the anatomical and functional state of the foot [3, 4]. This circumstance necessitates a critical analysis of the capabilities of individual approaches and their rational combination.

Clinical examination is used at the stage of primary diagnosis and provides a general idea of the morphology and function of the foot. It includes a questionnaire (complaints, medical history, footwear/load characteristics) and a direct examination of the patient [5, 6]. The examination is carried out both without load in a sitting position and under physiological load; the shape of the foot, the condition of the skin, the axis of the limb are assessed, and local structural changes in different regions of the foot are identified [2, 6, 7]. For functional assessment of the arches of the foot, tests are used (lever test of the first toe, active plantar flexion test of the toes, Stritter's test, "peeking toes" symptom, etc.) [8, 9].

Despite the importance of clinical assessment, its results largely depend on subjective factors — the patient's sensations and the doctor's interpretation [4, 6]. In order to improve data reproducibility, structured examination protocols have been proposed to improve data reproducibility (Papaliodis D.N. et al., 2014), including sequential assessment of the skin, structural abnormalities and deformities, foot sensitivity, the range of active and passive movements in the foot joints, and comprehensive palpation analysis [10]. However, even standardized schemes do not allow for an objective quantitative assessment of load parameters and functional dynamics, which makes it necessary to confirm clinical observations with instrumental methods.

One of the most common traditional approaches remains the morphometric method, based on direct measurements (length, width, height of the foot, calculation of indices) using a tape measure, podoscope, and compass. Its simplicity, accessibility, and speed make it convenient in clinical practice, but the method

reflects mainly static anatomical parameters and is subject to measurement errors [11].

Podometry, which involves the use of a podoscope or caliper to determine linear, angular, and volumetric characteristics, expands the capabilities of morphometric analysis. It allows for the detection of early stages of flat feet and the assessment of foot symmetry and shape [2]. However, like morphometry, podometry does not provide information about the functional state of the foot and remains dependent on subjective interpretation of measurements.

Plantography, a method of recording impressions of the plantar surface of the foot, has become an important step towards objectivity and effectiveness in assessing the condition of the foot. Analysis of plantograms (visual and calculated) using the Clark angle, Weissflog index, Chippaux–Smirak index, and other indicators allows for a comprehensive characterization of the condition of the foot arches and is a recognized method for detecting flat feet [2, 11–13]. The advantages of the method remain its accessibility and simplicity of measurement. However, the quality of the impressions obtained depends on many factors (technique, material, foot position), and low resolution and manual data processing reduce the accuracy and reproducibility of the results [14, 15]. Attempts at automation, such as devices like the Foot Imprinter (Orlin M.N., 2000), simplified the process but did not eliminate methodological limitations [16].

The transition to digital technologies has led to the emergence of a new field — computer plantography, which is an automated system for recording, analyzing, and storing data on the plantar surface of the foot [17]. Unlike traditional methods, computer plantography provides high measurement accuracy, eliminating the influence of subjective factors [3, 7, 18, 19]. A key advantage is the ability to quantitatively assess the distribution of load on the feet, which is particularly important in the diagnosis of musculoskeletal disorders (e.g., flat feet) and the selection of individual orthopedic devices. An additional advantage is the ability to repeat measurements multiple times, which allows tracking changes over time, for example, during rehabilitation or correction of flat feet in children [20, 21].

The development of the method is accompanied by the creation of specialized hardware and software complexes. For example, a computerized plantar complex developed in Volgograd in 2005, based on a



flatbed scanner and specialized software, automated the calculation of morphometric parameters (length, width, angles of deviation of the first and fifth toes, Weisflog index, etc.) and provided a qualitative assessment of the foot's support surface, including dynamic functional tests [22].

The "DiaSled" (footprint) complex allows for both static and dynamic analysis of the foot, assessing the duration and force of pressure on different parts of the foot, step parameters, and visualizing the results in the form of podograms, which makes it a sought-after tool for clinical assessment [23].

Modern automated podometry and plantography systems cover a wide range of devices, from domestic plantoscopes (GREENFOOT, PODOSKAN-MBN) [24], which record only the plantar surface, to multifunctional complexes such as BODYTRONIC 600 (Germany) [25] and domestic DiaSled-Scan and Scan [26], which allow additional visualization of the rear and lateral surfaces of the foot. Such an expansion of the diagnostic field increases the accuracy of the assessment of deformities and asymmetries. An important practical advantage of all digital systems is the high speed of examination, which makes them particularly useful for mass screening and in conditions of intensive clinical flow.

Thus, despite the relatively high cost of equipment and software, computer plantography has taken a firm place in modern foot diagnostics. Its main advantages — objectivity, high accuracy, and the ability to dynamically analyze load distribution — make the method optimal for specialized centers and, in the future, the basis for integrated digital systems for assessing the condition of the musculoskeletal system [3, 12].

Verification of foot pathologies and the choice of treatment tactics in many cases rely on radiological diagnostic methods. Among them, the most common is flat X-ray imaging, which still retains its status as the "gold standard" for visualizing bone structures. It allows for a detailed assessment of the anatomical structures of the foot both without load and under physiological load, which is especially important when analyzing biomechanics and planning the correction of deformities [26, 27].

A standard X-ray examination of the foot is performed in several projections. Direct and lateral X-rays in a standing position (with and without load) are used to assess the configuration of the tarsal and metatarsal bones, the transverse tarsal joint (Chopart joint),

the metatarsophalangeal joints (Lisfranc joint), and the phalanges of the toes [28]. A direct plantar projection is used to determine angular characteristics and interosseous relationships [29, 30]. The lateral projection allows measurement of the navicular angle, heel angle, height of the longitudinal arch, and angle of inclination of the forefoot, displaying the tarsal bones, calcaneus, and joints of the first toe [29, 30]. The oblique internal projection supplements the data, detailing the anatomy of the tarsus and metatarsus [29, 30]. Thus, radiography remains the main method of morphometric analysis of the skeletal skeleton of the foot, necessary for the diagnosis of deformities and evaluation of the effectiveness of surgical treatment [31, 32].

However, the methodological limitations of radiography — two-dimensionality and static images — do not allow for a complete analysis of spatial and functional characteristics. These shortcomings are partially compensated for by X-ray computed tomography (XCT), including weight-bearing computed tomography (WBCT), which has been in use since 2012 [27, 33]. WBCT provides three-dimensional reconstruction and layer-by-layer imaging of bone structures under physiological load, which significantly increases the accuracy of spatial measurements. The method is indispensable for assessing complex multiplanar deformities, but, like radiography, it remains static and is accompanied by exposure to ionizing radiation, which limits its use, especially in dynamic observation [33].

Magnetic resonance imaging (MRI) is preferred for studying soft tissue components. It provides high spatial resolution in the visualization of tendons, ligaments, fascia, vessels, and nerves, and allows for the diagnosis of inflammatory and degenerative changes without radiation exposure. MRI is especially valuable in cases of combined injuries and chronic pain syndromes. The main limitations of the method are its high cost, the duration of the examination, and the presence of contraindications (metal implants, claustrophobia, etc.) [34, 35].

Ultrasound examination (US) plays an important role in functional foot diagnostics due to its non-invasive nature, the possibility of dynamic scanning in real time, and the ability to perform interventional procedures. The method is informative in assessing the condition of soft tissue structures — tendons, fascia, and ligaments. Its main limitation is its high operator dependence, i.e., the subjectivity of interpretation,



which directly depends on the specialist's qualifications, reducing the reproducibility and objectivity of the results. It is a factor that stimulates the development of automated imaging systems and the search for more standardized alternatives [36–38].

Against this backdrop, non-contact digital technologies are actively developing, in particular 3D scanning, which is considered an accurate and reproducible method for obtaining morphometric data on the foot. Unlike traditional contact methods, 3D scanning allows the foot to be examined both statically and dynamically, providing a three-dimensional representation of shape, volume, and load distribution [39, 40]. The debate in the scientific community about its advantages over classical methods has stimulated a number of comparative studies.

The work of C.P. Witana et al. (2006) demonstrated statistically significant discrepancies between the results of manual measurements and 3D scanning: differences in 8 out of 18 spatial parameters of the foot indicated the greater accuracy of digital technologies [41].

A study by J. Zhao and S. Xiong (2008), focused on applied footwear design tasks, revealed minimal discrepancies (<5 mm) between 3D scanning and traditional methods, which became important evidence of the practical applicability of the technology in mass footwear production [42].

By 2010, the accumulated data set allowed a group of foreign researchers to conduct a review assessing the potential of 3D foot scanning for use in orthopedics, the footwear industry, and other ergonomic purposes. Based on a meta-analysis of 38 scientific articles, it was found that 3D scanning provides more accurate and rapid morphometric data on the foot compared to traditional methods, and also allows for the study of dynamic changes in the shape of the foot under load. The researchers also noted the practical effectiveness of 3D scanning for the personalized manufacture of footwear and orthopedic products, which reduces production times [43]. Further studies have reinforced these conclusions.

For example, L.K. Noldner and H.J.H. Edgar (2013), comparing 2D scanning, 3D scanning, and manual measurements, clearly identified 3D scanning as the method that minimizes measurement error and provides the highest accuracy in studying foot morphology [44]. The work of Yu-Chi Lee et al. (2014) expanded on this conclusion, proving that 3D scanning provides the most complete and informative set

of foot morphometric data not only in comparison with the method using a digital caliper, but also with digital and ink footprint methods [45]. Recent studies continue to demonstrate the reliability of the technology even in complex cases. A study by J. Mueller et al. (2023), focused on pediatric practice (277 children), confirmed the higher accuracy of 3D scanning for assessing anatomical parameters of the foot compared to 2D scanning and manual measurements, emphasizing its validity for clinical application [46].

The analysis of modern foot examination methods allows us to draw the following conclusions, which are of significant importance for science and clinical practice.

1. *Synergy of methods.* No single method provides comprehensive diagnostic information. The future of diagnostics lies in the strategic combination of traditional and digital technologies. Clinical examination remains the starting point, but requires further structuring to reduce subjectivity. X-ray imaging retains a key role in the assessment of bone pathology, but should be supplemented by CT for complex cases and 3D reconstruction. Functional assessment increasingly relies on computerized plantography and 3D scanning. MRI and ultrasound are the methods of choice for soft tissue pathology.

2. *Advantages of digitization.* Computer plantography and 3D scanning provide unprecedented accuracy, objectivity, and speed in obtaining morphometric and functional data, minimizing the human factor. They form the basis for the creation of extensive standardized databases necessary for scientific research and the development of standards.

3. *Personalization.* 3D technology opens up new horizons in personalized medicine, making it economically and technically feasible to manufacture individual orthoses, insoles, and shoes that precisely match the anatomy and biomechanics of a specific patient. This directly increases the effectiveness of conservative treatment and rehabilitation.

4. *Prospects.* The integration of data from various methods (e.g., combining load data from computer plantography with 3D scanning or WBCT) using artificial intelligence technologies for analysis is the most promising direction. This will not only improve diagnosis, but also predict the development of pathologies and optimize treatment strategies. Reducing the cost and increasing the accessibility of digital systems is a key task for their widespread implementation in routine clinical practice.



Thus, the future of foot diagnostics is determined not by replacement, but by the synergy of traditional and digital methods within a unified diagnostic ecosystem. This approach provides a comprehensive, objective, and personalized assessment of the condition of the foot, contributing to the effectiveness of prevention, treatment, and rehabilitation of patients.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

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The importance and principles of endovascular technologies and "hybrid approaches" in the treatment of occlusive lesions of lower extremity arteries

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ABSTRACT. The clinician must first understand the natural history of obliterative atherosclerosis and chronic limb threatening ischemia before making a decision regarding therapeutic or surgical treatment options. Clearly, mild ischemia as evidenced by claudication does not place the patient at significant risk for limb loss. The analysis of the literature shows that at the present time hybrid and endovascular approaches are applied more often, being an alternative to traditional surgeries. Most researchers have proved that while performing 'hybrid' and endovascular surgeries there is a very low incidence of cardiovascular issues and infectious complications, and in most cases, it is possible to save the limb. However, the principle and importance of the effectiveness of a particular method or approach of treatment of multilevel obliterative atherosclerotic lesions of lower limb arteries depends on the degree of limb ischemia as well as on the anatomical level of the lesion where revascularization is performed. We have already published many articles regarding the concept, advantages, comparisons of hybrid approach in Russian Highly Attested Commission Journals. This review article analyses and summarizes the possibilities of "hybrid" and endovascular approaches in the treatment of patients with multilevel obliterative atherosclerotic lesions, stenosis and chronic limb threatening ischemia.

Keywords: atherosclerosis, chronic limb threatening ischemia, hybrid operations, endovascular approach, limb salvage

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Значение и принципы применения эндоваскулярных технологий и «гибридных подходов» в лечении окклюзионных поражений артерий нижних конечностей

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РЕЗЮМЕ. Прежде чем принять решение о терапевтическом или хирургическом лечении, врач должен понять естественную историю облитерирующего атеросклероза и хронической угрожающей конечности ишемии. Очевидно, что легкая ишемия, проявляющаяся хромотой, не подвергает пациента значительному риску потери конечности. Анализ литературы показывает, что в настоящее время все чаще применяются гибридные и эндоваскулярные подходы, являющиеся альтернативой традиционным операциям. Большинство исследователей доказали, что при выполнении «гибридных» и эндоваскулярных операций очень низка частота сердечно-сосудистых проблем и инфекционных осложнений, а в большинстве случаев удается сохранить конечность. Однако принцип и значение эффективности того или иного метода либо подхода к лечению многоуровневых облитерирующих атеросклеротических поражений артерий нижних конечностей зависит от степени ишемии конечности, а также от анатомического уровня поражения, на котором выполняется реваскуляризация. Мы уже опубликовали множество статей о концепции, преимуществах, сравнительных характеристиках гибридного подхода в российских журналах высокой аттестации. В данной обзорной статье анализируются и обобщаются возможности «гибридного» и эндоваскулярного подходов в лечении пациентов с многоуровневыми облитерирующими атеросклеротическими поражениями, стенозами и хронической угрожающей ишемией конечности.

Ключевые слова: атеросклероз, хроническая угрожающая ишемия конечности, гибридные операции, эндоваскулярный подход, спасение конечности

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INTRODUCTION

In recent years, with increasing life expectancy, the number of patients with occlusive vascular diseases has increased significantly [1–4], among which atherosclerotic lesions occupy the major share and are registered in 14% of the population aged over 50 years [5–7].

To date, unsatisfaction with the results of treatment of patients with chronic limb threatening ischemia (CLTI) has led to the development and use of various methods of treatment of such group of patients [8, 9]. In particular, at the end of the XX century, gene therapy methods using stem cells, transposition of various tissues to the limb region [3, 4] were widely used, which, unfortunately, did not allow to fully achieve an adequate revascularization of the limb.

For a long time, bypass surgeries were the gold standard in the treatment of patients with lower limb arterial lesions [6, 7, 10–12]. At the same time, if bypass surgeries had a significant and lasting effect in proximal arterial lesions (category C and D according to TASC II classification), multilevel reconstructions with the use of several shunts were required in multistage arterial lesions [6–13]. As a rule, such operations were accompanied by the development of severe infectious complications in the postoperative period, both early and late. In the mid-90s of the last century, methods of endovascular treatment of patients with arterial lesions of various basins were actively introduced into practical angio-surgery. One of the first widely used methods was balloon angioplasty. However, its widespread use and hopes were replaced by a certain pessimism due to the low long-term efficacy of the method [14]. At the same time, the best results were achieved when angioplasty was supplemented with stenting [15].

At the same time, the multiple nature of vascular lesions, the severe condition of patients did not allow to perform in some cases only open or endovascular revascularization of the ischemic limb in isolation, which led to the emergence of a new trend in vascular surgery — hybrid operations, which are now widely spread in Russian Federation and whole world [16–21]. Currently, most specialists note that endovascular interventions are the “first line” of therapy in patients with CLTI [18–21]. The world's first hybrid operation was performed in 1973 by Porter and Dotter, who performed angioplasty of the iliac arteries followed by femoral-popliteal bypass. From 2014-year hybrid operations are performed every often in St. Petersburg City Limb Salvage Center, City hospital No. 14 and many more hospitals and Limb Salvage Centers in the Russian Federation. “Hybrid intervention” is a combination of various methods used in different sub-specialties. In particular, with regard to cardiovascular surgery, hybrid operations are understood as a

conceptually consistent combination of open surgical reconstruction with endovascular techniques performed simultaneously [22–25, 39, 40, 44, 45, 60, 61]. At present, the number of surgical interventions with hybrid approach in the treatment of patients with limb ischemia is significantly increasing, which is also reflected in the number of publications devoted to various aspects of its application [22, 23]. Thus, P.S. Aho and M. Venermo in 2012 [8], demonstrated that in the vascular surgery department of Helsinki University Central Hospital, the number of hybrid procedures increased from 4 in 2004 to 73 in 2011.

However, the indications for hybrid surgeries remain controversial with no clear international guidelines. Based on the cooperation of two surgical centers in the Czech Republic and Sweden P. Balaz et al. in 2012 [24] believe that hybrid operations should be performed: (1) in patients with chronic limb threatening ischemia (2) acute limb ischemia and (3) in occlusions of previously applied shunts (Fig. 1). Hybrid (simultaneous open surgical and endovascular) procedures require an operating room equipped with advanced imaging capability, such as digital subtraction angiography. On the patient's right side (R), open femoral endarterectomy with patch angioplasty is combined with retrograde placement of a balloon-expandable covered stent in the common iliac artery to treat severe combined common femoral artery and common iliac artery disease. On the patient's left side (L), external iliac artery stenosis and long-segment occlusion of the superficial femoral artery are treated by placement of a self-expanding stent in the external iliac artery and a femoral-to-popliteal bypass graft [70].

The multistage lesions of the lower limb arteries are one of the indications for hybrid operations, as they are accompanied by shorter hospitalization duration, significantly lower number of postoperative complications and mortality rate, and similar results compared to open interventions [11, 16, 17, 21, 26, 39, 40–45, 59–61]. At the same time, high surgical risk is considered to be the main factor in the choice of indications. At the same time, as the authors rightly point out, the presence of critical/chronic ischemia, diabetes, renal failure can compromise the results of hybrid surgery. The high efficacy of hybrid technology was also demonstrated by the study of A.A. Kuchay, A.N. Lipin et al. in 2023 and 2024, Jin Hyun Joh et al. in 2014 [7, 21, 28, 40], in which the comparison of primary patency in patients with hybrid and open surgery was 100 and 90.9%, respectively. However, the study and comparison of the results of using hybrid surgery and open operative tactics, according to the published study by Peter Balaz et al. in 2013 [27], did not allow us to unequivocally judge the effectiveness of one or the other method, since in many respects the treatment results depend on both the degree of limb ischemia

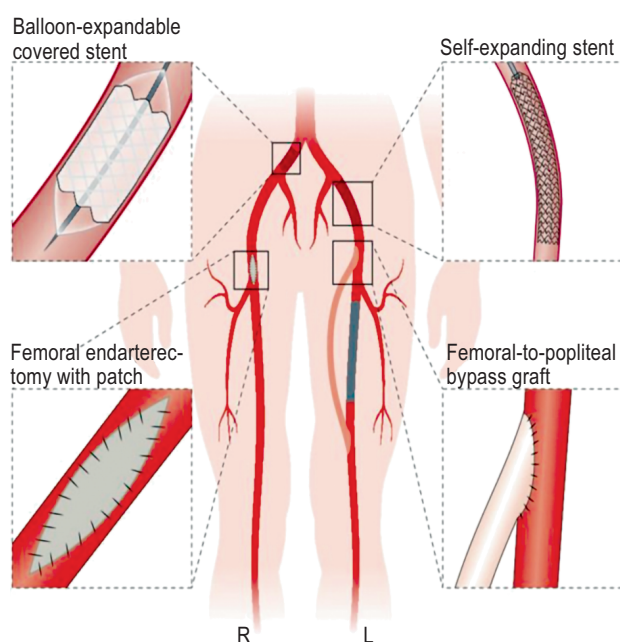


Fig. 1. Hybrid approaches for simultaneous, multilevel revascularization of advanced peripheral artery disease [70]

Рис. 1. Гибридные подходы для одновременной многоуровневой реваскуляризации прогрессирующего заболевания периферических артерий [70]

and the anatomical level of the lesion where endovascular recanalization was performed. In order to establish indications for a particular method of surgery, a combination of diagnostic invasive and non-invasive methods of investigation is currently used: duplex and triplex sonography, computed tomography (CT) angiography, magnetic resonance (MR) angiography. Nowadays magnetic resonance angiography (MRA) takes the main place in diagnostics of the level and degree of arterial channel lesions, the sensitivity and specificity of which reaches 99.5% and 98.8% respectively. At the same time, contrast angiography is the main method of investigation and confirmation of the operation result in almost all cases. However, computed tomography angiography (CTA) with 3D reconstruction allows to obtain the most complete information about the state of atherosclerotic lesion of the aorto-iliac segment, as well as to choose the diameter and length of the balloon, stent and catheter. The problem of performing one-stage combined operations is mainly of an organizational nature, as it requires a hybrid operating room, simultaneous presence of endovascular surgeon and a vascular surgeon in the operating room, or a vascular surgeon who is skilled in the technique of endovascular interventions. According to modern concepts, a hybrid operating theatre should be equipped with a high-quality angiographic system with high resolution and the ability to create high-quality images during

surgery. It should be noted that the hybrid approach in the treatment of patients with occlusive and stenotic lesions of the lower limb arteries should include cooperation of endovascular surgeons with angio-surgeons, as well as specially trained nursing staff.

HYBRID AND ENDOVASCULAR APPROACHES

The hybrid approach in critical or chronic ischemia surgery is highly controversial. It should be noted that there are different interpretations of hybrid surgery in the literature. Thus, D.P. Slovut in 2007 [32], published a “hybrid” approach in the treatment of patients with critical or chronic limb ischemia in whom it was impossible to use the patient’s autovenous vein due to its insufficient length. Consequently, the author performed atherectomy with the Silverhawk device and femoral-popliteal bypass in 4 observations. However, this approach in the treatment of critical ischemia patients is debatable, especially under the terminology of “hybrid”. For example, the hybrid approach is possible in patients with short arterial lesions [4]. In addition, in some cases it is necessary to perform angioplasty of arteries that are outflow pathways. Thus, M. Piazza et al in 2011 [35], A.A. Kuchay, A.N. Lipin et al. in 2019, 2021, 2022–2024 [7, 16, 17, 20, 21, 40, 44, 45, 59, 60, 69] showed that using a hybrid approach compared to open surgery significantly reduces the duration of the patient’s stay in the intensive care unit, in addition, the immediate and long-term results of operations are comparable. I.G. Uchkin in 2013 [37], A.A. Kuchay et al [44] highlights a number of advantages of hybrid operations: a lower degree of invasiveness; reduction in the length of implants used; the ability to overcome prolonged lesions (Table 1, Fig. 2).

R.W. Chang et al. in 2008 [36] in their study convincingly showed that the hybrid approach in the treatment of patients with occlusive diseases of lower limb arteries can be an alternative to open surgery. Thus, based on the analysis of treatment results of 171 patients who underwent endarterectomy from the common femoral artery and stenting of the iliac artery, they demonstrated that 30-day postoperative mortality was 2.3% and five-year survival rate was 60%. At the same time five-year primary patency rate of the reconstructed vessels reached 60% and secondary patency 98%. A similar opinion was demonstrated by D.P. Slovut et al. in 2009 [31], who noted that hybrid approach in the treatment of patients with occlusive diseases of lower limb arteries allows not only to reduce the incidence of complications, but also to improve the results of treatment, besides, as the authors note, the technical success of the procedure is very high. Thus, according to M. Matsagkas et al. in 2011 [38], the



Table 1

Important clinical, angiographic, and treatment outcomes to be considered in trials and registries. Evaluating endovascular devices for peripheral arterial disease and critical limb threatening ischemia

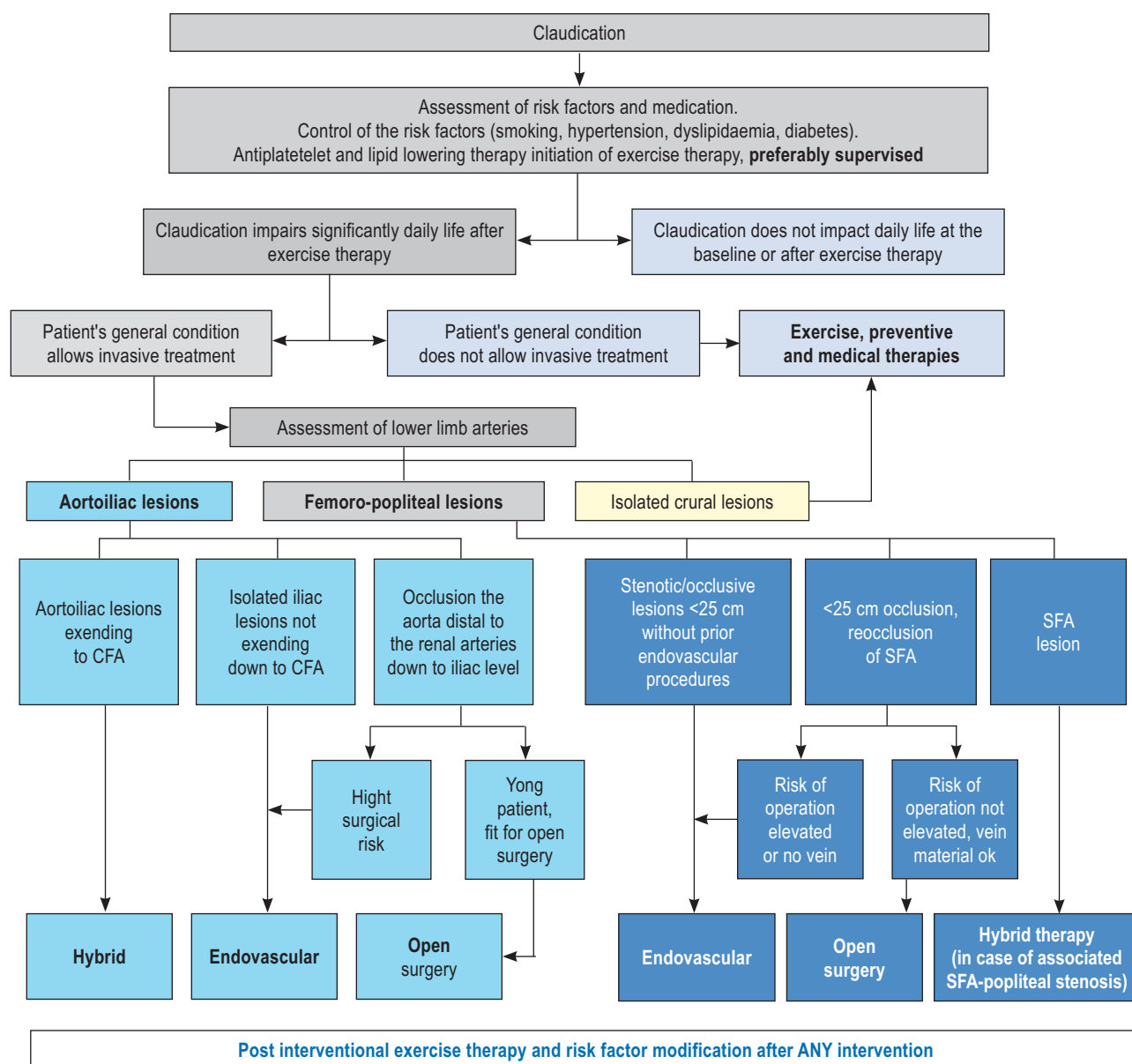
Таблица 1

Важные клинические, ангиографические и лечебные результаты, которые необходимо учитывать в исследованиях и реестрах.
Оценка эндоваскулярных устройств для лечения заболеваний периферических артерий и критической ишемии конечностей

Clinical characteristics	Angiographic characteristics	Outcomes
Demographics (age, sex, socioeconomic class)	Lesion location, length	Patency (primary, assisted primary, secondary)
Diabetes mellitus	Calcification	Clinically driven target lesion revascularization
Chronic kidney disease	Number of runoff	6-minute walk test
Rutherford class	Stenosis versus occlusion	Quality of life metrics
Ankle brachial index	De novo versus restenosis	Amputation free survival
Toe brachial index	–	Major adverse limb events
Comorbid coronary, cerebrovascular conditions	–	Time to wound healing
Wound location, size, and depth	–	Time to ambulation
Soft tissue/bone infection	–	Hospital length of stay
–	–	Readmission
–	–	Total medical expense

technical success of the procedure reached 98% in the authors' study, with primary and secondary patency at 24 months being 93.2% and 95.5%, respectively. However, factors such as the presence of diabetes mellitus and dyslipidemia may influence the decreased efficacy of treatment with the hybrid approach, as shown by G.A. Antoniou et al. in 2009 [30]. At the same time, V.I. Rusin et al. in 2014 [33], thanks to the use of hybrid technologies, preserved the limb in 85.7% of patients with critical ischemia during one year of follow-up. However, in a large single-center study published in 2014, M. Taurino et al. [34] stated that hybrid technologies are most effective in the treatment of patients with TASC II category C and D. According to the Russian guidelines for the management of patients with lower limb arterial diseases published in 2013, it is recommended to perform hybrid operations in multilevel lesions of lower limb arteries. It is believed that hybrid technologies can make a significant contribution to solving the problem of lower limb amputations, as by improving blood circulation, in some cases small amputations or necrectomy can be limited. At the same time, very compromising data of the hybrid approach are presented by Japanese authors M. Nakayama and F. Sakamoto in 2013 [29], whose study presented a group of 11 patients with occlusion of the superficial femoral artery, including the ostium, who underwent endovascular revascularization and endarterectomy from the ostium. In spite of the fact that all patients achieved improvement of the limb condition (pain reduction and wound healing), 9 of them died during the follow-up pe-

riod of 23.9 ± 14.7 months. At the same time, as the authors note, this was due to the initially severe condition of the patients. The work of V.V. Franz et al. in 2011 [41], who applied a hybrid technique — femoral-popliteal bypass with stenting of the deep femoral artery with titanium nickelide TH-10 construction, can be considered as very original research in the study of hybrid revascularization. The technique applied by the authors improved the blood supply to the limb by 31% in terms of clinical parameters compared to the control group. Up to the present time in the literature concerning the problem of surgical treatment of patients with lower limb ischemia there is no unambiguous answer concerning the first-priority choice of the method of limb revascularization. This is primarily determined by the type of lower limb arterial channel lesion, the level of occlusion or stenosis, the presence of severe comorbid status, surgeon's experience and technical equipment of clinics. Open revascularization of the limb even in high-risk patients is of great importance. This is primarily due to well-developed techniques and indications for various types of surgeries, as well as the results of their application, especially femoral-popliteal [42], aorto-femoral and femoral-tibial bypass [16, 17, 20, 21, 40, 43, 44], as well as revascularization using complex non-standard methods of surgery, including lumbar sympathectomy, spinal cord stimulation and gene therapy [66]. However, there are factors that account for the ambiguity of results and are independent of the severity of ischemia and anatomic localization. Another aspect is that one of the debated issues



CFA = common femoral artery; SFA = superficial femoral artery.

^a Related to atherosclerotic lower extremity artery disease (LEAD).

Fig. 2. Management of patients with intermittent claudication [68]

Рис. 2. Ведение пациентов с перемежающейся хромотой [68]

in open surgery is the choice of graft for limb revascularization. Despite the indisputable advantages of autovenous grafting, alternative shunts are still being searched for. The main disadvantage of open surgeries, according to the majority of studies, is their high traumatic nature and duration, possibility of wound and prosthesis infection, thrombosis of vascular prostheses in the distant period, development of restenosis, false aneurysms of anastomoses, etc. In many respects, these disadvantages of open operations led to the search and development of endovascular technologies [46], which

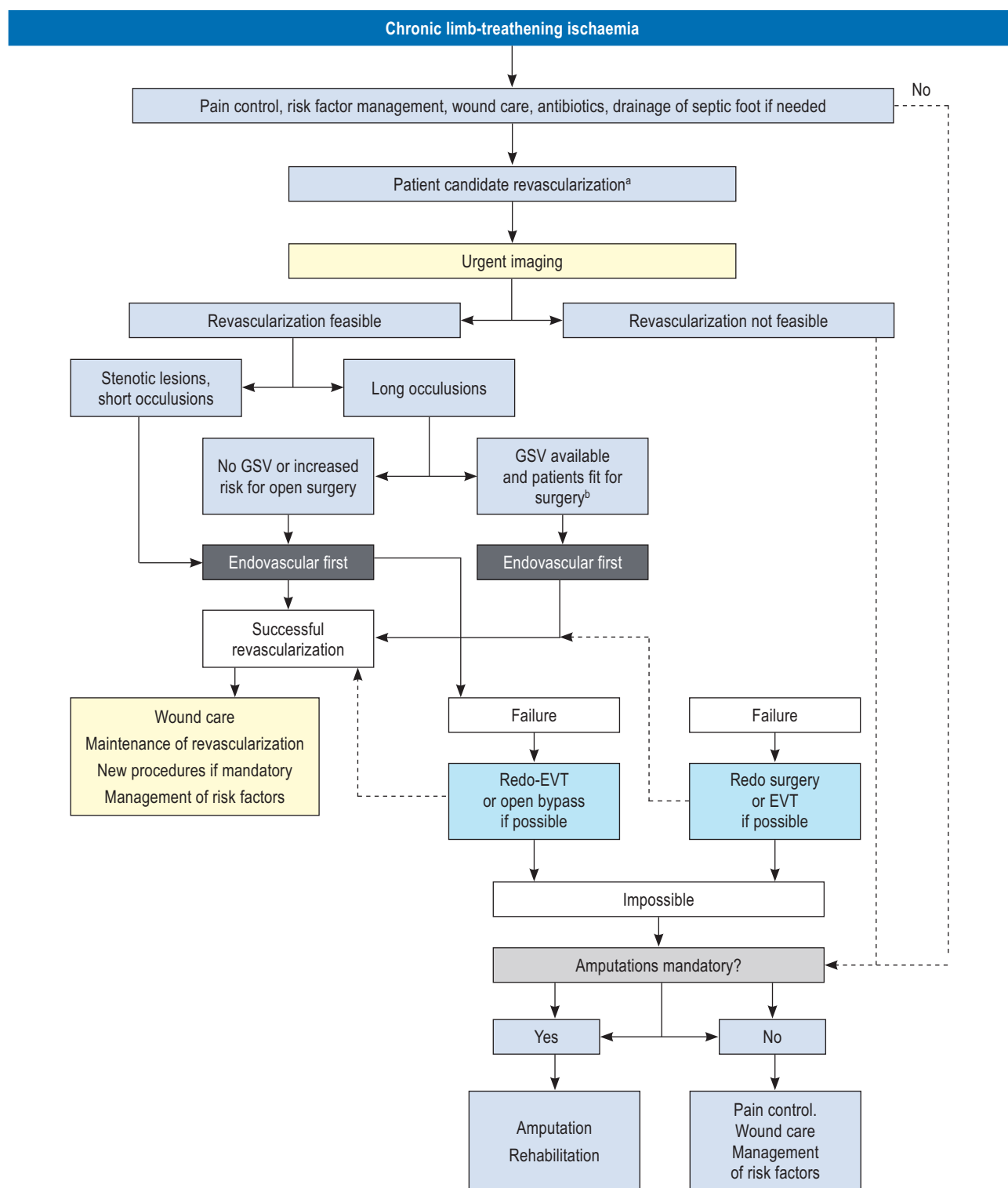
are also not without disadvantages and are accompanied by the development of such complications as stent restenosis [49, 67]. Despite the wide introduction of endovascular technologies and quite a significant number of publications comparing advantages and disadvantages of both endovascular and open interventions, the question of which technology is more effective is still open, even in spite of rather stable recommendations on the choice of revascularization method published in the TASC II consensus document in 2007. In spite of the fact that this document can be considered outdated to a



greater extent, despite the fact that it is practically fundamental for the choice of the method of limb revascularization, it still requires revision in the light of the development and achievement of new results of endovascular interventions in chronic limb ischemia. In this regard, on the pages of the European Journal of Vascular Surgery the president of the European Society of Vascular and Endovascular Surgeons spoke about significant disagreements on the drafting of a new consensus document by the world's leading specialists and societies of vascular surgeons of the USA and Europe, which also does not make corrections in the definition of both promising directions in the development of vascular surgery of critical limb ischemia and in the choice of the method of its treatment [48]. The increase in the frequency of endovascular interventions for peripheral arterial diseases was convincingly demonstrated by D.L. Cull et al. in 2010 [47]. Thus, according to their data, the frequency of endovascular revascularization of the lower limbs increased by 33% from 1995 to 2005, which is also indicated by other authors. The most studied aspect of treatment of patients with limb ischemia is the comparison of angioplasty and stenting results, when comparing which significantly better results were obtained using the stenting technique. However, this method is also not without disadvantages, which is associated with the development of stent reclosures or restenosis in the medium and long term. In addition, ambiguous results are obtained when performing angioplasty and stenting of outflow arteries, in particular, the arteries of the lower leg, especially in the presence of atypical anatomy and diabetes mellitus. At the same time, as A.A. Kuchay, A.N. Lipin et al in 2019 and D.V. Ovcharenko et al. in 2009 [45, 64] note, subintimal angioplasty is a valuable tool in the arsenal of an endovascular surgeon, as it allows to restore patency of extended chronic occlusions with minimal costs. N. Fernandez et al. in 2010 [65], A.A. Kuchay, A.N. Lipin et al in 2019, 2024 [44, 45] also demonstrated that after endovascular interventions on the lower leg arteries there is a high frequency of repeated re-interventional operations. As noted by N.U. Saqib in 2013 [56], endovascular interventions on the lower leg arteries in some cases are the only possible treatment method to save the limb from amputation. A number of authors have shown that endovascular interventions for critical ischemia of the lower limbs in patients with diabetic foot syndrome are effective and justified, allowing to perform economical resection interventions on the foot and to stop the phenomena of critical ischemia [55]. The number of works on this issue increases every year. In a meta-analysis published by G.A. Antoniou et al. in 2013 [50] comparing the results of endovascular versus open surgeries in occlusive stenotic lesions of the femoral-popliteal arterial segment, it was shown that the choice in favor of endovascular interven-

tions should be preferred in patients with severe comorbid status, as endovascular surgeries are less traumatic, which is also indicated by a number of other authors. Thus, to date, the choice of treatment technology in the lesion of the popliteal artery with involvement of the femoral artery or tibial arteries is debatable. As noted by M.B. Malas et al. in 2014 [54], bypass surgeries for lesions of the femoral-popliteal segment are performed in patients with more severe and multilevel lesions of atherosclerosis, which largely determines in some cases worse results of conventional surgical treatment in comparison with endovascular revascularization of the limb. T. Kudo et al. in 2006 [51] when comparing the results of treatment of patients with critical ischemia concluded that in recent years arterial angioplasty has been used more often than open revascularization, besides, the authors made a very controversial conclusion about the expediency of primary endovascular interventions compared to open operations. At the same time, the latter are assigned such indications for application as impossibility of endovascular revascularization or high probability of absence of clinically significant results. It should be noted that the results of endovascular interventions are still ambiguous. Thus, D.T. Baril et al. in 2010 [57] noted that the use of endovascular technologies in TASC II type C lesions require further study of the long-term results of treatment. According to one of the large studies BASIL (Bypass versus Angioplasty in Severe Ischemia of the Leg), which compared the results of endovascular treatment methods and bypass surgeries, summarized by M.S. Conte in 2010 [53], it is shown that, to date, the results of surgeries with the use of autovenous surgeries are superior to endovascular surgeries. It is now recognized that endovascular techniques are most effective when applied to stenoses or occlusions of the aorto-iliac segment [52, 58]. However, according to the systematic review by V. Jongkind et al. in 2010 [58], primary arterial patency after endovascular interventions is inferior to open surgical revascularization, although secondary patency almost reaches the same level as after open surgery.

At the same time, according to R. Pulli et al. in 2011 [63], the rate of reinterventions after endovascular surgeries for iliac arterial segment lesions varies from 2.5 to 12.5% within 2 to 60 months and depends on the severity of the condition, type of arterial lesion and its level. In turn, B.L. Chen in 2011 [62] believes that angioplasty of the iliac arteries can be the first line of choice for surgical treatment of such patients. In recent years, in endovascular treatment of patients with critical ischemia or intermittent claudication, drug-eluting or cutting-coated balloons, new generation stents and stent grafts: biodegradable, drug-eluting stents and others have been increasingly used, which allows



EVT = endovascular therapy; GSV = great saphenous vein.

^a In bedridden, demented and/or frail patients, primary amputation should be considered.

^b In the absence of contra-indication for surgery and in the presence of adequate target for anastomosis/runoff.

Fig. 3. Management of patients with chronic limb threatening ischemia [68]

Рис. 3. Ведение пациентов с хронической ишемией, угрожающей потерей конечности [68]



to significantly improve the results of treatment of this group of patients (Fig. 3).

CONCLUSION

Hybrid technique in obliterative atherosclerosis in lower limb arteries having multilevel lesions is most effective than open and endovascular techniques. It has shorter duration of surgical intervention with very low blood loss, short time in intensive care unit, very low complications rate. Hybrid interventions make it possible in all cases to eliminate ischemia symptoms and save the patients limb, while reducing complication rate and lethality, which is especially important in patients with high surgical risk due to severe concomitant pathology. In conclusion, it should be noted that the final conclusions about the feasibility and efficacy of a particular method of revascularization can be made only on the basis of the principles of evidence-based medicine after several randomized trials.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Competing interests. The authors declare that they have no competing interests.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Review



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Application of the Fracking hydraulic rupture technique in chronic calcified occlusion of the common femoral artery

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ABSTRACT. The patency achieved by conventional peripheral interventions for atherosclerotic lesions in the common femoral artery (CFA), called the "no stenting zone", is not superior to that achieved by surgical endarterectomy due to calcified plaque occupying the area. Plaque modification strategies to obtain acute gain in CFA patency provide the better clinical outcomes than standard balloon angioplasty. Atherectomy devices, which focus on the modification of superficial calcifications, contribute to the improvement of clinical outcomes. However, deep calcifications resist vessel expansion such that luminal gain is not easily achieved. This case report demonstrates the successful application of the "Fracking" technique (hydraulic plaque disruption) for recanalizing a heavily calcified chronic occlusion of the common femoral artery (CFA) in a 61-year-old male patient presenting with critical limb ischemia (CLI) of the left lower extremity and a trophic ulcer at the Limb Salvage Center (St. Petersburg State Healthcare Institution "City Hospital No. 14"). Conventional antegrade and retrograde endovascular recanalization attempts failed. Under fluoroscopic guidance, direct percutaneous puncture of the occluded CFA segment was performed using an 18G needle connected to an inflation device. Controlled injection of contrast medium at low pressure (2–3 atm) created dissection planes within the calcified plaque, establishing a channel. Subsequent antegrade balloon angioplasty of the CFA and stenting of the external iliac artery restored flow, resolving rest pain and enabling healing of the trophic ulcer. This technique represents a viable endovascular salvage option for calcified occlusions resistant to standard methods and can serve as an alternative to open surgery when contraindicated.

Keywords: atherosclerosis, critical ischemia, endovascular surgery, calcification

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Обзор

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Применение методики гидравлического разрыва Fracking при хронической кальцинированной окклюзии общей бедренной артерии

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РЕЗЮМЕ. Проходимость, достигаемая при традиционных периферических вмешательствах по поводу атеросклеротических поражений в общей бедренной артерии (ОБА), называемая «зоной без стентирования», не превосходит проходимость, достигаемую при хирургической эндартерэктомии, из-за наличия кальцинированных бляшек в этой области. Стратегии модификации бляшек для достижения улучшения проходимости ОБА обеспечивают лучшие клинические результаты, чем стандартная баллонная ангиопластика. Устройства для атерэктомии, которые фокусируются на модификации поверхностных кальцификаций, способствуют улучшению клинических результатов. Однако глубокие кальцификации препятствуют расширению сосуда, поэтому увеличение просвета сосуда достигается с трудом. В данном клиническом случае продемонстрировано успешное применение методики «фрекинга» (гидравлическое разрушение бляшки) для реканализации сильно кальцинированной хронической окклюзии ОБА у 61-летнего мужчины с критической ишемией конечности левой нижней конечности и трофической язвой в Центре спасения конечностей (СПБ ГБУЗ «Городская больница № 14»). Традиционные антеградные и ретроградные эндоваскулярные попытки реканализации оказались неудачными. Под флюороскопическим контролем была выполнена прямая чрескожная пункция окклюзированного сегмента ОБА с использованием иглы 18G, соединенной с устройством для нагнетания контрастного вещества. Контролируемое введение контрастного вещества под низким давлением (2–3 атм) создало плоскости расслоения внутри кальцинированной бляшки, сформировав канал. Последующая антеградная баллонная ангиопластика ОБА и стентирование наружной подвздошной артерии восстановили кровоток, устранили боли в покое и позволили заживить трофическую язву. Данная методика представляет собой жизнеспособный вариант эндоваскулярного лечения кальцинированных окклюзий, устойчивых к стандартным методам, и может служить альтернативой открытой хирургической операции при наличии противопоказаний.

Ключевые слова: атеросклероз, критическая ишемия, эндоваскулярная хирургия, кальциноз

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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INTRODUCTION

Atherosclerotic peripheral artery disease (PAD), especially when it manifests as critical limb ischemia (CLI), is still remains a major cause of major limb amputation and disability in patients. Patients with CLI often have multilevel arterial disease, including severely calcified areas [1–10]. Endovascular interventions are the preferred first-line treatment for limb revascularization. However, chronic total occlusions (CTOs), especially in the common femoral artery (CFA), with severe calcification pose a serious technical challenge. Standard antegrade and retrograde recanalization techniques often prove ineffective for passing through rigid calcified plaques [11–13]. Open common femoral artery endarterectomy is a highly effective method of treating lesions in this location, but it is associated with a higher risk of complications and may be contraindicated in patients with severe concomitant pathology. This necessitates the search for alternative endovascular strategies for calcified occlusions of the CFA. The Fracking technique (hydraulic plaque fracturing) has been described as a potential solution in such complex situations [14, 15].

AIM

The aim is to present a clinical case demonstrating the successful application and technical details of the hydraulic fracturing (Fracking) for recanalization of calcified chronic total occlusion of the common femoral artery in a patient with critical lower limb ischemia, when standard endovascular approaches were ineffective, emphasizing the role of Fracking as a limb-saving procedure and an alternative to open surgery.

MATERIALS AND METHODS

A case report describing the treatment of a patient with obliterating atherosclerosis of the lower extremities with critical ischemia of the left lower extremity and a trophic ulcer of the left lower leg.

CLINICAL CASE PRESENTATION

Based on the patient's medical history, clinical findings, and medical records, the following results were obtained.

A 61-year-old patient K., was admitted to the emergency room of St. Petersburg City Hospital No. 14 on

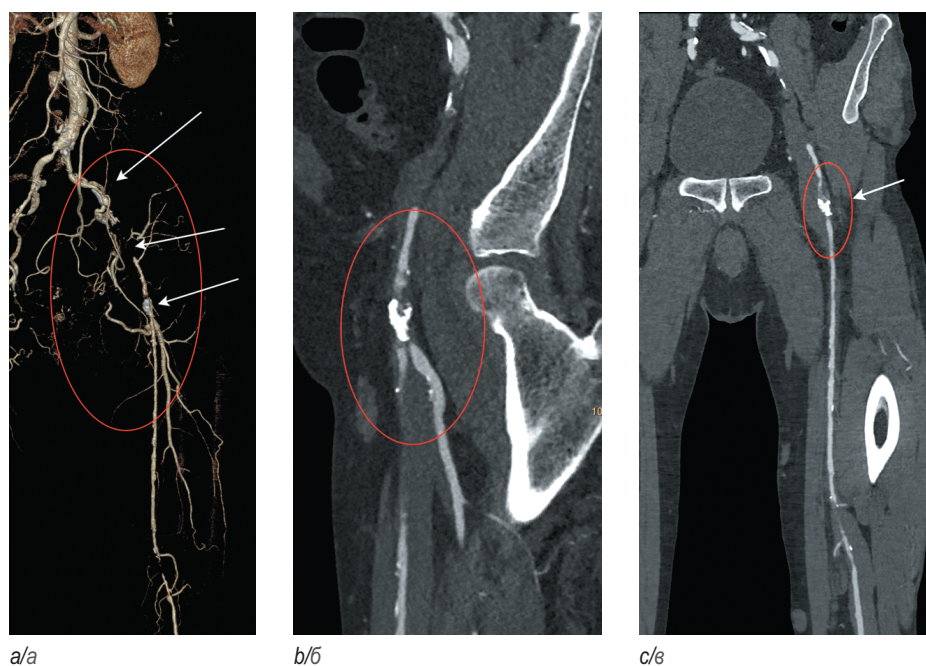


Fig. 1. Multislice spiral computed tomography angiography (a) and multi-planar analysis of the iliac-femoral (b) and femoral-popliteal segments (c) (from the personal archive of the REDL doctor N.N. Gruzdev)

Рис. 1. Мультиспиральная компьютерная ангиография (а) и мультипланарный анализ подвздошно-бедренного (б) и бедрено-подколенного сегментов (в) (из личного архива врача РЭДЛ Груздева Н.Н.)

April 24, 2025, complaining of pain at rest in his left lower limb and a chronic non-healing trophic ulcer on his left lower leg. Medical history: long-standing obliterating atherosclerosis of the lower extremities (OASLE), no previous medical care, no surgeries. In the fall of 2024, his condition worsened with increased pain and the appearance of trophic disorders on the left lower leg. He was hospitalized on an emergency basis.

Primary clinical diagnosis: obliterating atherosclerosis of the lower extremity arteries. Critical ischemia of the left lower extremity. Stage IV chronic arterial insufficiency (CAI). Trophic ulcer of the left lower leg. Lymphangitis.

Concomitant pathology. Ischemic heart disease. Atherosclerosis of the coronary and cerebral vessels. Stage II hypertension, risk of cardiovascular complications (CCO) — 4, chronic heart failure (CHF) — functional class (FC) II. Cerebrovascular disease. Grade II mixed-origin discirculatory encephalopathy (DE).

Examined, the following data obtained.

Complete blood count: leukocytes — $7.7 \times 10^9/L$, erythrocytes — $5.05 \times 10^{12}/L$, hemoglobin — 159 g/L, platelets — $284 \times 10^9/L$. Leukocyte formula: stab neutrophils — 3%, segmented neutrophils — 64%, lymphocytes — 25%, monocytes — 8%.

Serum biochemistry revealed elevated creatinine levels — 127.33 $\mu\text{mol}/L$.

ABI (ankle-brachial index): left — 0.37.

MSCT angiography: left — common iliac artery (CIA) — no significant stenosis, external iliac artery (EIA), common femoral artery — occluded, deep femoral artery (DFA) — no significant stenosis, superficial femoral artery (SFA) — short occlusion in the distal third, popliteal artery (PA), anterior tibial artery (ATA), tibiofibular trunk (TFT), fibular artery (FA), posterior tibial artery (PTA) — no significant stenosis (Fig. 1).

Considering the clinical and angiographic findings, a decision was made to perform revascularization of the arteries of the left lower extremity.

Retrograde left brachial arterial access was obtained, and a 5F introducer was inserted. The abdominal aorta was catheterized, and selective angiography was performed (Figs. 2, 3).

A 6.7F guide introducer was inserted and positioned in the left CIA. Using a 0.035" hydrophilic, rigid guide-wire supported by a 6.0 mm balloon catheter, recanalization of the EIA was performed, with exit into the true



Fig. 2. Selective angiography. Occlusion of the external iliac artery, common femoral artery on the left (yellow oval) (from the personal archive of the REDL doctor N.N. Gruzdev)

Рис. 2. Селективная ангиография. Окклюзия наружной подвздошной артерии, общей бедренной артерии слева (желтый овал) (из личного архива врача РЭДЛ Груздева Н.Н.)

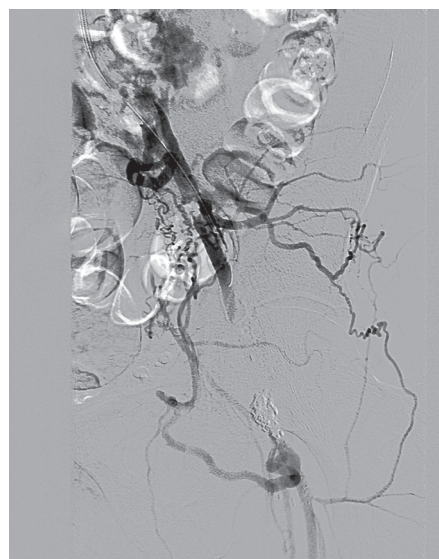


Fig. 3. Selective angiography. Recanalization of the external iliac artery was performed, selective angiography through a balloon catheter, calcified occlusion of the common femoral artery, deep femoral artery and superficial femoral artery are filled due to collaterals from the proximal third (from the personal archive of the REDL doctor N.N. Gruzdev)

Рис. 3. Селективная ангиография. Выполнена реканализация наружной подвздошной артерии, селективная ангиография через баллон-катетер, кальцинированная окклюзия общей бедренной артерии, глубокая бедренная артерия и поверхностная бедренная артерия заполняются за счет коллатералей от проксимальной трети (из личного архива врача РЭДЛ Груздева Н.Н.)

lumen in the distal third of the EIA. Attempts at ante-grade recanalization of the CFA were unsuccessful.

Retrograde puncture of the DFA was performed in the proximal third using a 0.014" nitinol guidewire and a support catheter, and an attempt was made to perform retro-

grade recanalization of the distal occlusion of the CIA, but it was unsuccessful (Figs. 4, 5). A decision was made to perform hydraulic fracturing of the calcified CIA occlusion.

Method: Under fluoroscopic guidance, an 18G needle connected to a syringe deflator with contrast

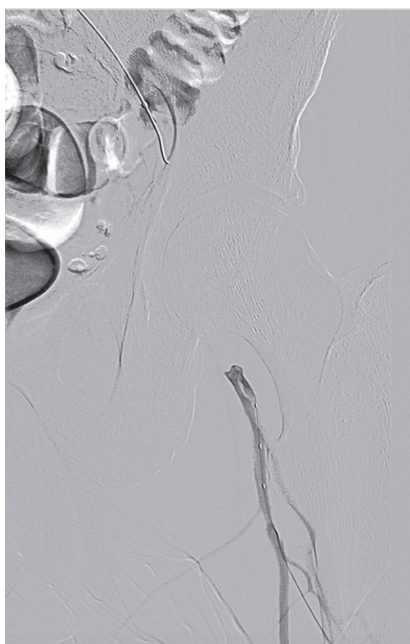


Fig. 4. Instruments in the deep femoral artery (from the personal archive of the REDL doctor N.N. Gruzdev)

Рис. 4. Инструменты в глубокой бедренной артерии (из личного архива врача РЭДЛ Груздева Н.Н.)

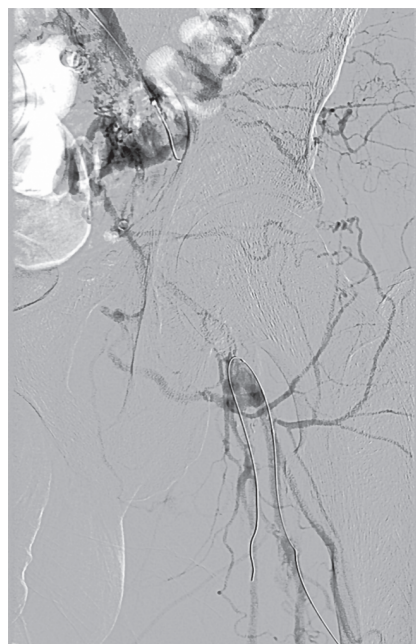


Fig. 5. Retrograde recanalization of the common femoral artery, dropping of instruments into the deep femoral artery (from the personal archive of the REDL doctor N.N. Gruzdev)

Рис. 5. Ретроградная реканализация общей бедренной артерии, «сваливание» инструментов в поверхностной бедренной артерии (из личного архива врача РЭДЛ Груздева Н.Н.)

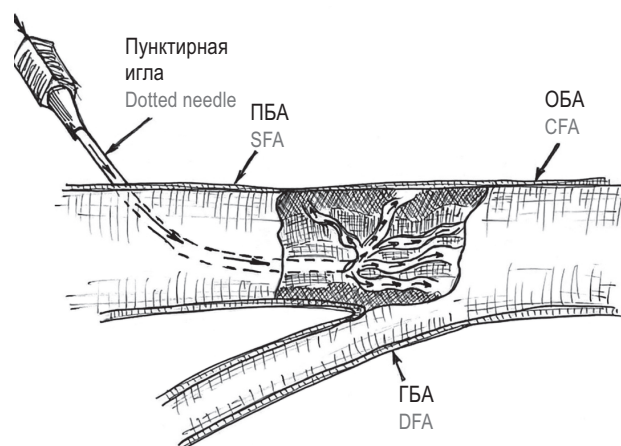


Fig. 6. Hydraulic fracturing method Fracking: DFA — deep femoral artery; CFA — common femoral artery; SFA — superficial femoral artery (scheme by N.N. Gruzdev)

Рис. 6. Методика гидравлического разрыва Fracking: ГБА — глубокая бедренная артерия ОБА — общая бедренная артерия; ПБА — поверхностная бедренная артерия (схема Груздева Н.Н.)



Fig. 7. Puncture of the common femoral artery with an 18G needle (from the personal archive of the REDL doctor N.N. Gruzdev)

Рис. 7. Пункция общей бедренной артерии иглой 18G (из личного архива врача РЭДЛ Груздева Н.Н.)

medium was used to puncture the atherosclerotic plaque (ASP) in the CFA, with gradual injection of contrast under a pressure of 2–3 atm until the pressure in the deflator syringe dropped, indicating delamination of the atherosclerotic plaque (Fig. 6).

The procedure was repeated along the course of the CFA occlusion (Figs. 7, 8). Figure 8 shows the channel formed in the CFA.

Subsequently, antegrade instrument insertion was performed through the formed channel in the DFA and balloon angioplasty of the CFA and DFA with a 5.0 mm balloon, with removal of instruments from the DFA with endovascular hemostasis of retrograde puncture of the DFA (Fig. 9).

Balloon angioplasty of the CFA and external iliac artery (EIA) was performed with stenting of the EIA using a 7.0–100.0 mm nitinol self-expanding stent, with balloon post-dilatation using a 7.0 mm balloon. During follow-up angiography: patent blood flow through the CIA, EIA, CFA, DFA (no extravasation). The EIA was diffusely stenosed throughout its entire length, up to subocclusion in the distal third, PA, ATA, TFT, FA — without significant stenosis (Fig. 10).

Taking into account the data of the control angiography, clinical picture, and local status, an intraoperative decision was made to complete the surgical intervention without balloon angioplasty of the EIA. Dynamic

monitoring of the patient's condition and the dynamics of the local wound process was recommended.

In the postoperative period, the patient demonstrated an improvement in his condition: pain at rest was relieved, and there were positive dynamics in the wound process. Ultrasound Dopplerography of the arteries of the lower extremities was performed. CFA, DFA — main altered blood flow (Fig. 11). Local status: the wound has cleared, inflammation has been relieved, and active granulation is occurring (Fig. 12). The patient was discharged for outpatient treatment.

CONCLUSION

A clinical case study demonstrates the successful application of hydraulic fracturing to treat chronic calcified occlusion when other methods have failed. The technique may serve as a valuable alternative to open reconstruction when the latter is not feasible.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

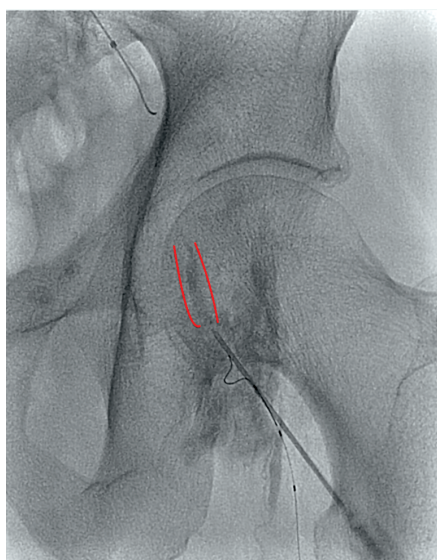


Fig. 8. Channel formed in the common femoral artery (from the personal archive of the REDL doctor N.N. Gruzdev)

Рис. 8. Сформирован канал в общей бедренной артерии (из личного архива врача РЭДЛ Груздева Н.Н.)

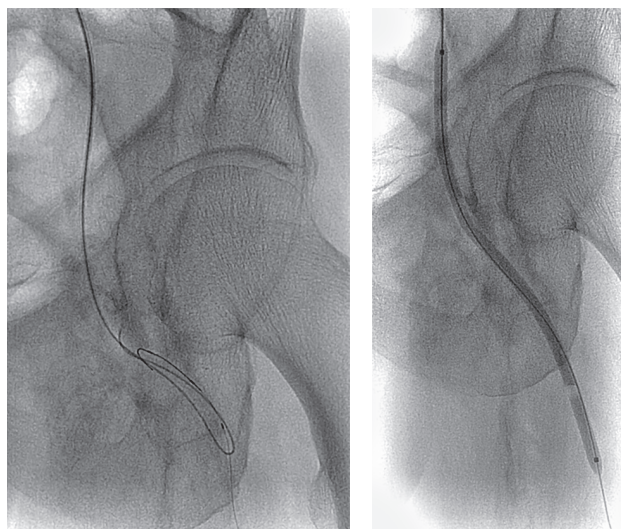


Fig. 9. Antegrade placement of instruments through the formed channel (from the personal archive of the REDL doctor N.N. Gruzdev)

Рис. 9. Антеградное заведение инструментов через сформированный канал (из личного архива врача РЭДЛ Груздева Н.Н.)

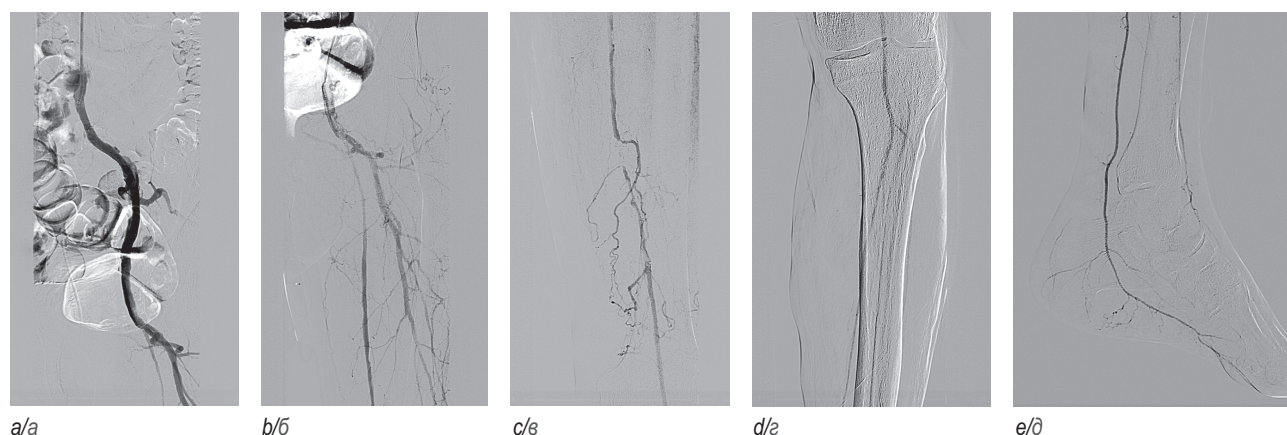


Fig. 10 Control angiograms (a–e) (from the personal archive of the REDL doctor N.N. Gruzdev)

Рис. 10. Контрольные ангиограммы (a–d) (из личного архива врача РЭДЛ Груздева Н.Н.)

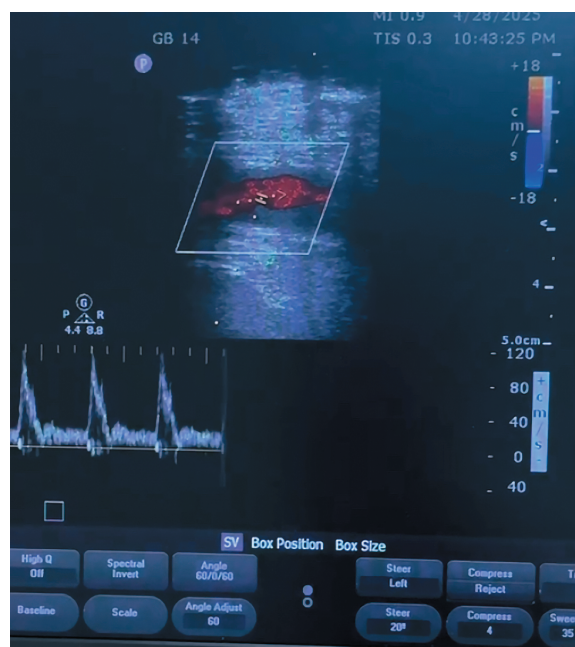


Fig. 11. Blood flow according in common femoral artery (from the personal archive of the REDL doctor N.N. Gruzdev)

Рис. 11. Кровоток по общей бедренной артерии (из личного архива врача РЭДЛ Груздева Н.Н.)



Fig. 12. Local status (from the personal archive of the REDL doctor N.N. Gruzdev)

Рис. 12. Местный статус (из личного архива врача РЭДЛ Груздева Н.Н.)

Competing interests. The authors declare that they have no competing interests.

Consent for publication. Written consent was obtained from the patient for publication of relevant medical information within the manuscript.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведе-

ние исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Информированное согласие на публикацию. Авторы получили письменное согласие пациента на публикацию медицинских данных.



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Alexander Vladimirovich Ivanov — outstanding Russian ophthalmologist-pathologist

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ABSTRACT. The article is devoted to the life and creative path of the outstanding Russian ophthalmologist-pathologist, scientist, educator, organizer and founder of the national histology and pathological anatomy of the organ of vision, Doctor of Medicine, Professor Alexander Vladimirovich Ivanov, who was born in 1836 in Kursk and came from the bourgeoisie of the Tauride province. In 1859, he graduated from the Medical Faculty of the Imperial Moscow University. During his studies, he was diagnosed with pulmonary tuberculosis, which accompanied him throughout his life, despite the fact that he repeatedly traveled to France for treatment. From 1859 to 1867, A.V. Ivanov was fortunate to work in various laboratories of famous professors in Würzburg, Heidelberg, Wiesbaden, Vienna and Berlin, where he improved his knowledge in ophthalmology. Over these years of hard work, he became an excellent pathologist widely known in Europe. In 1867, at the St. Petersburg Medical and Surgical Academy, with the support of Professor E.A. Yunge, A.V. Ivanov successfully defended his doctoral dissertation on the topic “Materials on the normal and pathological anatomy of the lens”. From 1869 to 1876, the scientist worked at the Department of Ophthalmology as an extraordinary and ordinary professor at the Kiev University of St. Vladimir and at the same time became the first head of the eye department at the Kiev Military University. Professor Ivanov’s scientific interests during his short but bright life focused mainly on the normal and pathological anatomy of the eye, and he made significant achievements in this area. In 1876, due to an exacerbation of the tuberculosis process in the lungs, the scientist went to France for treatment. A.V. Ivanov died on October 27, 1880 in Menton (France) at the age of 44 from pulmonary tuberculosis complicated by pulmonary hemorrhage. He was buried in the Russian Orthodox cemetery “Old Castle” in Menton.

Keywords: Alexander Vladimirovich Ivanov, ophthalmologist-pathologist, educator, organizer, founder of the national histology and pathological anatomy of the organ of vision, Professor, scientist, Doctor of Medicine

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РЕЗЮМЕ. Статья посвящена жизненному и творческому пути выдающегося российского офтальмолога-патолога, ученого, педагога, организатора и основоположника отечественной гистологии и патологической анатомии органа зрения, доктора медицины, профессора Александра Владимировича Иванова, родившегося в 1836 году в Курске и происходившего из мещанской семьи Таврической губернии. В 1859 году он окончил медицинский факультет Императорского Московского университета. Во время учебы у него был диагностирован туберкулез легких, который сопровождал его на протяжении всей жизни, несмотря на то что он неоднократно ездил на лечение во Францию. С 1859 по 1867 годы А.В. Иванову повезло работать в различных лабораториях известных профессоров в Вюрцбурге, Гейдельберге, Висбадене, Вене и Берлине, где он совершенствовал свои знания в области офтальмологии. За эти годы напряженной работы он стал отличным патологоанатомом, широко известным в Европе. В 1867 году в Санкт-Петербургской Медико-хирургической академии при поддержке профессора Е.А. Юнге А.В. Иванов успешно защитил докторскую диссертацию на тему «Материалы по нормальной и патологической анатомии хрусталика». С 1869 по 1876 годы ученый работал на кафедре офтальмологии в качестве экстраординарного и ординарного профессора Киевского университета Святого Владимира и одновременно стал первым заведующим офтальмологической кафедрой Киевского военного университета. Научные интересы профессора Иванова в течение его короткой, но яркой жизни были сосредоточены в основном на нормальной и патологической анатомии глаза, и он добился значительных успехов в этой области. В 1876 году в связи с обострением туберкулезного процесса в легких ученый отправился на лечение во Францию. А.В. Иванов скончался 27 октября 1880 года в Ментоне (Франция) в возрасте 44 лет от туберкулеза легких, осложненного легочным кровотечением. Он был похоронен на русском православном кладбище «Старый Замок» в Ментоне.

Ключевые слова: Александр Владимирович Иванов, офтальмолог-патолог, педагог, организатор, основоположник национальной гистологии и патологической анатомии органа зрения, профессор, ученый, доктор медицины.

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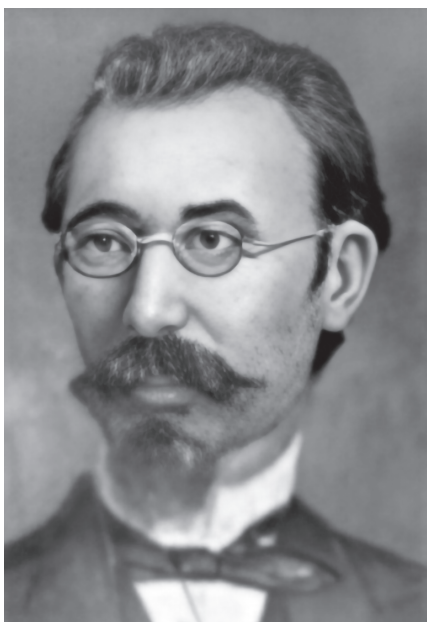


Fig. 1. Ivanov Alexander Vladimirovich (14.09.1836–27.10.1880)

October 27, 2025 marks the 145th anniversary of the death of the outstanding Russian ophthalmologist-pathologist, scientist, educator and organizer, Doctor of Medicine, Professor Alexander Vladimirovich Ivanov, a student of the German anatomist Heinrich Müller (Fig. 1) [1].

A.V. Ivanov was born on September 14 (new style), 1836 in the city of Kursk, who came from the bourgeoisie of the Taurida province. He graduated from the Kursk Gymnasium and in 1859 from the Medical Faculty of the Imperial Moscow University (Fig. 2)¹ [2].

In connection with the diagnosis of pulmonary tuberculosis during his student years, he decided to go abroad for treatment to the city of Montpellier with its Mediterranean climate, which is known to have a beneficial effect on the respiratory and cardiovascular systems, and at the same time continued to practice ophthalmology there².

In Montpellier, Alexander Vladimirovich met Friedrich Alexander Hermann Pagenstecher, a prominent ophthalmologist, eye surgeon, medical writer and founder of the ophthalmological clinic in Wiesbaden, who had a serious influence on his choice of specialty [3]. In fact, from 1859 to 1867, this was his first trip abroad, during which A.V. Ivanov improved in ophthalmology, namely: he studied the normal and pathological anatomy of the

eye in the laboratory of Heinrich Müller in Würzburg, whom he considered his teacher, worked in the clinics of such famous professors as Jacob Hermann Knapp (Heidelberg), Friedrich Alexander Hermann Pagenstecher (Wiesbaden), Carl Ferdinand von Arlt (Vienna), Albrecht Friedrich Wilhelm Ernst von Gräfe (Berlin), where he practiced ophthalmology³. Over the years of his work in these prestigious laboratories, A.V. Ivanov has become an excellent pathomorphologist, widely known in Europe.

In 1867, after returning to Russia, A.V. Ivanov arrived at the Ophthalmology Department of the St. Petersburg Medical and Surgical Academy, headed by Eduard Andreevich Junge (Fig. 3). Professor Junge provided the necessary assistance in a short period of time, and with his support, A.V. Ivanov successfully defended his doctoral dissertation on the topic of "Materials for the normal and pathological anatomy of the lens" and was awarded the academic degree of Doctor of Medicine in the same year [4, 5].

Immediately after defending his dissertation, A.V. Ivanov was sent on a second foreign mission, where for two years he continued to improve his knowledge of the pathological anatomy of the eye and, as a result of his persistent work, gained worldwide fame.

After completing of his second trip abroad, on September 15, 1869, A.V. Ivanov was elected an extraordinary, and in 1875 — ordinary professor at the Ophthalmology Department of the Kiev University of St. Vladimir and at the same time became the head of the Eye Department of the Kiev Military University (Fig. 4). While working at Kiev University, Professor A.V. Ivanov, as the first head of the Eye Diseases Department, established himself as a brilliant lecturer, ophthalmic surgeon and follower of the traditions of the E.A. Junge scientific school. At that time, eye diseases were taught in the 3rd and 4th courses, lectures on ophthalmology were given for 3 hours a week in a specially adapted room.

The clinic had an outpatient clinic and a 10-bed inpatient department. Despite the rather difficult conditions, the treatment work was carried out in a well-coordinated manner. So, during the years of Professor A.V. Ivanov's tenure as head, 20,120 patients were admitted to the outpatient clinic (an average of 2,560 patients per year), and 1,259 patients passed through the hospital, 90% of whom were operated on.

Professor Ivanov's scientific interests throughout his relatively short but vibrant life have focused mainly on the normal and pathological anatomy of the eye, and his scientific and practical activities have been marked by the following achievements [6]: his unique pathoanatomical studies concern all membranes and tissues of the eye

¹ Ivanov Alexander Vladimirovich (ophthalmologist). Wikipedia. Available at: [https://ru.wikipedia.org/wiki/Иванов,_Александр_Владимирович_\(офтальмолог\)](https://ru.wikipedia.org/wiki/Иванов,_Александр_Владимирович_(офтальмолог)) (accessed 07/19/2025).

² Ivanov Alexander Vladimirovich. Wikisource. Available at: https://ru.wikisource.org/wiki/РБС/ВТ/Иванов,_Александр_Владимирович (accessed 07/21/2025).

³ Alexander Vladimirovich Ivanov. People's History. Available at: <https://biografie.narod.ru/medicine/ophthalmologist/ivanov/index.htm> (accessed 07/19/2025).



Fig. 2. Medical Faculty of the Imperial Moscow University. A.V. Ivanov's education from 1854 to 1859



Fig. 3. Naval and Land Clinical Hospital of the St. Petersburg Medical and Surgical Academy (1867)

(conjunctiva, cornea, iris, ciliary body, lens, choroid, optic nerve, retina, vitreous body); the pathological anatomy of trachoma and the pathohistological structure of phlyctenae developing on the mucous membrane of the eye and cornea in tuberculous-allergic keratoconjunctivitis have been thoroughly studied, and it has been proven that the main element characteristic of this disease is a nodule

consisting of a round-cell lymphocytic infiltrate with an admixture of epithelioid and plasma-type cells, while a structure similar to a tuberculous tubercle is detected, but without caseous decay and the presence of the pathogen; the anatomical picture of the iris, the angle of the anterior chamber in humans, birds and a number of animals was studied in detail in the historical aspect; the



Fig. 4. Kiev University of St. Vladimir. A.V. Ivanov worked there from 1869 to 1876

structural features of the ciliary muscle ("Ivanov's muscle") were described depending on its function with different refraction of the eye, cystic changes in the retina in the area of the serratus muscle on the extreme periphery of the fundus, which is currently of great importance for explaining the pathogenesis of the development of retinal detachment in people suffering from myopia, the network of nerve plexuses with nodes of nerve cells in the choroid, which are still important for explaining neurohumoral disorders and the pathogenesis of glaucoma, a case of glioma endophitum, etc. [7].

Otto Becker, a well-known eye pathologist and Professor at Heidelberg University, once highly praised the work of A.V. Ivanov and noted in his lectures that A.V. Ivanov alone had done more for the pathological anatomy of the eye than all other researchers combined. The high authority of A.V. Ivanov among German ophthalmologists is also evidenced by the fact that the famous German ophthalmologist Duke Karl-Theodor in Bavaria worked under his leadership [8].

The scientist was distinguished by his love for his specialty, rare diligence, a brilliant expert in the pathological anatomy of the eye, an experienced teacher and an excellent practical physician [9].

A.V. Ivanov is the author of 24 scientific works published mainly in the foreign press in German, including three manuals "Practical Ophthalmology" (1879), "Manual of Ophthalmology" (1880) and "Course of eye operations" (1881), written and published with the participation of A.V. Khodi¹.

In 1876, due to the exacerbation of the pulmonary tuberculosis process, the scientist went to France for treatment.

Four years later, Alexander Vladimirovich Ivanov, the founder of the national histology and pathological anatomy of the vision organ, died on October 27, 1880 in Menton (France) at the age of 44 from pulmonary tuberculosis complicated by pulmonary hemorrhage. He was buried at the Russian Orthodox cemetery "Old Castle" in Menton.

ADDITIONAL INFORMATION

The author read and approved the final version before publication.

Competing interests. The author declares the absence of obvious and potential conflicts of interest related to the publication of this article.

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Автор прочитал и одобрил финальную версию перед публикацией.

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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ПРАВИЛА ДЛЯ АВТОРОВ

Утв. приказом и.о. ректора
ФГБОУ ВО СПбГПМУ Минздрава России от 05.04.24

НАСТОЯЩИЕ ПРАВИЛА ДЛЯ АВТОРОВ ЯВЛЯЮТСЯ ИЗДАТЕЛЬСКИМ ДОГОВОРом

Условия настоящего Договора (далее «Договор») являются публичной офертой в соответствии с п. 2 ст. 437 Гражданского кодекса Российской Федерации. Данный Договор определяет взаимоотношения между редакцией журнала «**Russian Biomedical Research**» (далее по тексту «Журнал»), зарегистрированного Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций (РОСКОМНАДЗОР), свидетельство: ПИ № ФС77-74228 от 02 ноября 2018 г. (ранее ПИ № ТУ78-01869 от 17 мая 2016 г.), именуемой в дальнейшем «Редакция» и являющейся структурным подразделением ФГБОУ ВО СПбГПМУ Минздрава России, и автором и/или авторским коллективом (или иным правообладателем), именуемым в дальнейшем «Автор», принявшим публичное предложение (оферту) о заключении Договора.

Автор передает Редакции для издания авторский оригинал или рукопись. Указанный авторский оригинал должен соответствовать требованиям, указанным в разделах «Представление рукописи в журнал», «Оформление рукописи». При рассмотрении полученных авторских материалов Журнал руководствуется «Едиными требованиями к рукописям, представляемым в биомедицинские журналы» (Intern. committee of medical journal editors. Uniform requirements for manuscripts submitted to biomedical journals. Ann Intern Med. 1997;126:36–47).

В Журнале печатаются ранее не опубликованные работы по профилю Журнала.

Журнал не рассматривает работы, результаты которых по большей части уже были опубликованы или описаны в статьях, представленных или принятых для публикации в другие печатные или электронные средства массовой информации. Представляя статью, автор всегда должен ставить редакцию в известность обо всех направлениях этой статьи в печать и о предыдущих публикациях, которые могут рассматриваться как множественные или дублирующие публикации той же самой или очень близкой работы. Автор должен уведомить редакцию о том, содержит ли статья уже опубликованные материалы, и предоставить ссылки на предыдущую, чтобы дать редакции возможность принять решение, как поступить в данной ситуации. Не принимаются к печати статьи, представляющие собой отдельные этапы незавершенных исследований, а также статьи с нарушением «Правил и норм гуманного обращения с биообъектами исследований».

Размещение публикаций возможно только после получения положительной рецензии.

Все статьи, в том числе статьи аспирантов и докторантов, публикуются бесплатно.

Подача статей в журнал «Russian Biomedical Research» осуществляется по адресу электронной почты avas7@mail.ru с пометкой «**для Russian Biomedical Research**» или через сайт <https://ojs3.gpmu.org/index.php/biomedical-research>.

Требования к отправке статей

Перед заполнением анкеты авторам рекомендуется подготовить все необходимые для ввода данные, а также выбрать автора (в случае коллектива авторов статьи), ОТВЕТСТВЕННОГО ЗА ПЕРЕПИСКУ. Для успешного заполнения анкеты необходимо иметь всю указанную информацию и на русском, и на английском языках.

Все названия на английском языке, включая названия статьи, названия учреждений, их подразделений должны приводиться с прописных букв (например: Sex Differences In Aging, Life Span And Spontaneous Tumorigenesis; Bulletin of Experimental Biology and Medicine; Saint Petersburg State Pediatric Medical University) и непременно в соответствии с официальными наименованиями без самостоятельности.

Анкетные данные всех авторов — Имя Отчество Фамилия (полностью), ученая степень, звание, должность, место работы (кафедра, отделение), название учреждения, адрес учреждения, e-mail, ORCID, SPIN-код, телефон, ФИО автора, ответственного за переписку, и т.д. — заполняются в соответствующих полях формы заявки. Резюме, ключевые слова и название статьи также заполняются онлайн.

Статья должна соответствовать правилам оформления статей к публикации (см. ниже).

К каждой статье прилагается файл Экспертного заключения (ЭЗ). Для авторов СПбГПМУ ЭЗ может только подписываться авторами статьи, печать необязательна. Для авторов других учреждений ЭЗ оформляется обязательно полностью, с печатями (круглая печать учреждения) и подписями руководителей и комиссий данного учреждения. Заполненный, подписанный и «опечатанный» бланк ЭЗ для отправки онлайн предварительно сканируется или фотографируется. Образец ЭЗ можно скачать (https://gpmu.org/science/pediatricsmagazine/Russian_Biomedical_Research, Бланк экспертного заключения).

Отправленные анкетные данные авторов, статья, ЭЗ поступают на E-mail автору-отправителю (для подтверждения и проверки отправки) и на E-mail редакции scrcenter@mail.ru техническому редактору журнала «Russian Biomedical Research», с которым осуществляется вся дальнейшая работа по подготовке статьи в печать. Все вопросы по отправке статей можно адресовать на электронный адрес scrcenter@mail.ru техническому редактору журнала «Russian Biomedical Research» Марии Александровне Пахомовой.



Рукопись считается поступившей в Редакцию, если она представлена комплектно и оформлена в соответствии с описанными требованиями. Предварительное рассмотрение рукописи, не заказанной Редакцией, не является фактом заключения между сторонами издательского Договора.

При представлении рукописи в Журнал Авторы несут ответственность за раскрытие своих финансовых и других конфликтных интересов, способных оказать влияние на их работу. В рукописи должны быть упомянуты все лица и организации, оказавшие финансовую поддержку (в виде грантов, оборудования, лекарств или всего этого вместе), а также другое финансовое или личное участие.

В конце каждой статьи обязательно указываются вклад авторов в написание статьи, источники финансирования (если имеются), отсутствие конфликта интересов, наличие согласия на публикацию со стороны пациентов.

Правила оформления статей к публикации

Статья предоставляется в электронной форме (файл MS Word версии не старше 2003, т.е. с расширением doc), шрифт — 14, интервал — полуторный.

Файл статьи называется по Фамилии первого автора, например, Иванов.doc или Petrov.doc. Никаких других слов в названии не должно быть!

Ориентировочные размеры статьи, включая указатель литературы, таблицы и резюме, — 10–12 страниц текста через полтора интервала или 20–25 тысяч знаков с пробелами. Рекомендуемый размер обзора — 18–20 страниц «машинописного» текста или 35–40 тысяч знаков с пробелами. Примерное число литературных ссылок для экспериментальной статьи — 20, для обзоров и проблемных статей — 50.

Файл статьи должен содержать

НА РУССКОМ И АНГЛИЙСКОМ ЯЗЫКАХ:

- Заглавие (Title) должно быть кратким (не более 120 знаков), точно отражающим содержание статьи.
- Сведения об авторах (публикуются). Для каждого автора указываются: фамилия, имя и отчество, место работы, почтовый адрес места работы, e-mail, ORCID, SPIN-код. Фамилии авторов рекомендуется транслитерировать так же, как в предыдущих публикациях, или по системе BGN (Board of Geographic Names), см. сайт <http://www.translit.ru>.
- Резюме (Abstract) (1500–2000 знаков, или 200–250 слов) помещают перед текстом статьи. Резюме не требуется при публикации рецензий, отчетов о конференциях, информационных писем.

Авторское резюме к статье является основным источником информации в отечественных и зарубежных информационных системах и базах данных, индексирующих журнал. Резюме доступно на сайте журнала «Russian Biomedical Research» и индексируется сетевыми поисковыми системами. Из аннотации должна быть понятна суть исследования, нужно ли обращаться к полному тексту статьи для получения более подробной, интересующей его информации. Резюме должно излагать только существенные факты работы.

Рекомендуемая структура как аннотации, так и самой статьи IMRAD (для оригинальных исследований структура обязательна): введение (Introduction), материалы и методы (Materials and methods), результаты (Results), обсуждение (Discussion), выводы (Conclusion). Предмет, тему, цель работы нужно указывать, если они не ясны из заглавия статьи; метод или методологию проведения работы целесообразно описывать, если они отличаются новизной или представляют интерес с точки зрения данной работы.

Объем текста авторского резюме определяется содержанием публикации (объемом сведений, их научной ценностью и/или практическим значением) и должен быть в пределах **200–250 слов (1500–2000 знаков)**.

- Ключевые слова (Keywords) от 3 до 10 ключевых слов или словосочетаний из 2–4 слов, которые будут способствовать правильному перекрестному индексированию статьи, помещаются под резюме с подзаголовком «Ключевые слова». Используйте термины из списка медицинских предметных заголовков (Medical Subject Headings), приведенного в Index Medicus (если в этом списке еще отсутствуют подходящие обозначения для недавно введенных терминов, выберите наиболее близкие из имеющихся). Ключевые слова разделяются запятой.

- Текст статьи может быть написан либо на русском, либо на английском языке, также возможна публикация статьи с полным переводом. На русском и английском языках необходимо предоставить все рисунки и таблицы (заголовки, все надписи, а также текст таблиц должны иметь перевод).

В разделе «Методика» обязательно указываются сведения о статистической обработке экспериментального или клинического материала. Единицы измерения даются в соответствии с Международной системой единиц — СИ. Фамилии иностранных авторов, цитируемые в тексте рукописи, приводятся в оригинальной транскрипции.

Таблицы и рисунки приводятся непосредственно в теле статьи, каждый из которых имеет номер и название с обязательными ссылками на них в тексте статьи — в контексте предложения (например: «...как показано на рисунке 1...») или в конце предложения в круглых скобках (например: «...выявлена положительная корреляционная связь умеренной степени ($r=0,41$) между уровнем ТТГ матери и новорожденного (рис. 2)»; просьба учитывать, что в печатной версии журнала рисунки будут воспроизводиться в черно-белом варианте).

- Список литературы обязательно приводится в порядке упоминания.

Текст статьи должен быть подготовлен в строгом соответствии с настоящими правилами и тщательно выверен автором. В случае обнаружения значительного количества опечаток, небрежностей, пунктуационных и орфографических ошибок, нерасшифрованных сокращений, отсутствия основных компонентов, переводов заголовков таблиц, подрисунков подписей, надписей на рисунках, текста таблиц и других технических дефектов оформления статей редакция возвращает статью автору для доработки. Небольшие

погрешности редакция может исправить сама без согласования с автором. Редакция оставляет за собой право осуществления литературного и технического редактирования статей.

Сокращений, кроме общеупотребительных, следует избегать. Сокращения в названии статьи, названиях таблиц и рисунков, в выводах недопустимы. Если аббревиатуры используются, то все они должны быть непременно расшифрованы полностью при первом их упоминании в тексте (например: «Наряду с данными о РОН (резидуально-органической недостаточности), обуславливающей развитие ГКС (гиперкинетического синдрома), расширен диапазон исследований по эндогенной природе данного синдрома»).

Все цитирования производятся следующим образом:

ФИО автора, год издания и прочая информация не упоминаются в тексте. Вместо этого указывается ссылка на источник литературы в виде номера в квадратных скобках (пример: «Ряд исследователей отмечает различные нарушения речевых функций при эпилепсии в детском возрасте [17, 21, 22].»), который включен в расставленный в порядке упоминания (1, 2, 3 и т.д.) список источников в конце статьи.

Все ссылки должны иметь соответствующий источник в списке, а каждый источник в списке — ссылку в тексте.

В виде исключения в тексте могут приводиться ФИО конкретных авторов в формате И.О. Фамилия, год и даже название источника, но при этом все равно обязательна ссылка (в квадратных скобках в конце предложения) на источник, включенный в список литературы. (Например: «В 1892 году великий Эраст Гамильтонский описал в своем бессмертном труде «Об открытии третьего уха у человека» третье (непарное ухо)» [34].)

Литература (References)

Учитывая требования международных систем цитирования, список литературы приводится не только в обычном виде, но также и дополнительно в переведенном на английский язык (References).

В статье приводятся ссылки на все упоминаемые в тексте источники.

Фамилии и инициалы авторов в пристатейном списке приводятся в порядке упоминания.

В описании указываются все авторы публикации.

Библиографические ссылки в тексте статьи даются в квадратных скобках.

Ссылки на неопубликованные работы не допускаются.

Список литературы комплектуется в следующем порядке:

Нормативные акты

Приказы, нормативные акты, методические письма и прочие законные акты, патенты, полезные модели не вносятся в список литературы, оформляются в виде сносок. Сноска — примечание, помещаемое внизу страницы (постраничная сноска). Знак сноски ставят цифрой после фрагмента основного текста, где есть упоминание об этих источниках. Рекомендуются сквозная нумерация сносок по тексту.

Интернет-ресурс

1. Интернет-ресурс, где есть название источника, автор, вносится в список литературы (в порядке алфавита) с указанием даты обращения (см. ниже пример оформления).

2. Если есть только ссылка на сайт, оформляется подстрочное примечание (сноска), с указанием даты обращения.

Щеглов И. Насколько велика роль микрофлоры в биологии вида-хозяина? Живые системы: научный электронный журнал. Доступен по: http://www.biorf.ru/catalog.aspx?cat_id=396&d_no=3576 (дата обращения: 02.07.2012).

Kealy M. A., Small R. E., Liamputtong P. Recovery after caesarean birth: a qualitative study of women's accounts in Victoria, Australia. BMC Pregnancy and Childbirth. 2010. Available at: <http://www.biomedcentral.com/1471-2393/10/47/> (accessed: 11.09.2013).

Примеры оформления литературы

Книга:

Юрьев В.К., Моисеева К.Е., Глущенко В.А. Основы общественного здоровья и здравоохранения. Учебник. СПб.: СпецЛит; 2019.

Никифоров О.Н., ред. Санкт-Петербург в 2021 году. СПб.: Петростат; 2022.

Brandenburg J.H., Ponti G.S., Worring A.F. eds. Vocal cord injection with autogenous fat. 3 rd ed. NY: Mosby; 1998.

Domeika M. Diagnosis of genital chlamydial infection in humans as well as in cattle. Uppsala; 1994.

Глава из книги:

Тутельян В.А., Никитюк Д.Б., Шарафетдинов Х.Х. Здоровое питание — основа здорового образа жизни и профилактики хронических неинфекционных заболеваний. В кн.: Здоровье молодежи: новые вызовы и перспективы. Т. 3. М.; 2019: 203–227.

Статья из журнала:

Карсанов А.М., Полунина Н.В., Гогичаев Т.К. Безопасность пациентов в хирургии. Часть 2: Программа менеджмента качества хирургического лечения. Медицинские технологии. Оценка и выбор. 2019;1(35):56–65. DOI: 10.31556/2219-0678.2019.35.1.056-065.

Brandenburg J.H., Ponti G.S., Worring A.F. Vocal cord injection with autogenous fat: a long-term magnetic resonance. Laryngoscope. 1996;106(2,pt 1):174–80.

Deb S., Campbell B.K., Pincott-Allen C. et al. Quantifying effect of combined oral contraceptive pill on functional ovarian reserve as measured by serum anti-Müllerian hormone and small antral follicle count using three-dimensional ultrasound. Ultrasound Obstet Gynecol. 2012;39(5):574–580.

Тезисы докладов, материалы научных конференций:

Марковская И.Н., Завьялова А.Н., Кузнецова Ю.В. Микробный пейзаж пациента первого года жизни с дисфагией, длительно находящегося в ОРИТ. XXX Конгресс детских гастроэнтерологов России и стран СНГ: тез. докл. М.; 2023: 29–31.

Салов И.А., Маринушкин Д.Н. Акушерская тактика при внутриутробной гибели плода. В кн.: Материалы IV Российского форума «Мать и дитя». Ч. 1. М.; 2000: 516–519.

Авторефераты:

Авилов А.Ю. Девиации полоролевой идентичности мужчин с умственной отсталостью в условиях психоневрологического интерната. Автореф. дис. ... канд. психол. наук. СПб.; 2021.



Описание интернет-ресурса:

Естественное движение населения. Москва: Росстат. Доступен по: <https://rosstat.gov.ru/folder/12781> (дата обращения: 23.10.2023).

World Health Organization. Prevalence and incidence of selected sexually transmitted infections — 2008. Geneva: World Health Organization; 2012. Available at: https://aefsg.ch/wp-content/uploads/who-9789241503839_eng.pdf (accessed: 11.04.2024)

Перевод и транслитерация

В зависимости от ситуации следует либо проводить транслитерацию (писать исходные неанглоязычные слова буквами романского алфавита), либо указывать перевод неанглоязычной информации о первоисточниках в References.

Если цитируемая статья написана **на латинице** (на английском, немецком, испанском, итальянском, финском, датском и других языках, использующих романский алфавит), ссылку на нее следует привести на оригинальном языке опубликования. Пример (статья в норвежском журнале на норвежском языке):

Ellingsen A.E., Wilhelmsen I. Sykdomsangst blant medisinske jusstudenter. Tidsskr Nor Laegeforen. 2002;122(8):785–787. (In Norwegian).

Если статья написана **не на латинице** (на кириллице, в том числе на русском), нужно привести официальный перевод или выполнить транслитерацию в романский алфавит. Для книг необходимо в этом случае привести транслитерацию на латиницу. В конце описания в скобках указать язык издания.

Ссылка на источник литературы в References может состоять одновременно и из транслитерированных элементов (например, ФИО авторов, названия журналов), и из переводных (название публикации).

Стандарт транслитерации. При транслитерации рекомендуется использовать стандарт BSI (British Standard Institute, UK). Для транслитерации текста в соответствии со стандартом BSI можно воспользоваться ссылкой <http://ru.translit.ru/?account=bsi>.

ФИО авторов, редакторов. Фамилии и инициалы всех авторов на латинице следует приводить в ссылке так, как они даны в оригинальной публикации. Если в оригинальной публикации уже были приведены на латинице ФИО авторов, в ссылке на статью следует указывать именно этот вариант (независимо от использованной системы транслитерации в первоисточнике). Если в официальных источниках (на сайте журнала, в базах данных, в том числе в eLIBRARY) ФИО авторов на латинице не приведены, следует транслитерировать их самостоятельно по стандарту BSI.

Название публикации. Если у цитируемой Вами работы существует официальный перевод на английский язык или англоязычный вариант названия (его следует искать на сайте журнала, в базах данных, в том числе в eLIBRARY), следует указать именно его. Если в официальных источниках название публикации на латинице не приведено, следует выполнить транслитерацию в романский алфавит по стандарту BSI.

Название издания (журнала). Некоторые неанглоязычные научные издания (журналы) имеют кроме названия на родном языке официальное «параллельное» название на английском (например, у журнала «Сахарный диабет» есть официальное англоязычное название «Diabetes Mellitus»). Таким образом, для списка References в ссылке на статью из русско-

язычного журнала следует указать либо транслитерированное название журнала, либо переводное. Переводное название журнала можно взять либо с официального сайта журнала (или использовать данные о правильном написании англоязычного названия из цитируемой статьи), либо проверить его наличие в базе данных, например в CAS Source Index, библиотеке WorldCat или каталоге Web of Science (ISI), каталоге названий базы данных MedLine (NLM Catalog). В случае, когда у журнала нет официального названия на английском языке, в References нужно приводить транслитерацию по системе BSI. Не следует самостоятельно переводить названия журналов.

Место издания. Место издания в ссылках всегда следует указывать на английском языке и полностью — не в транслитерации и без сокращений. То есть Moscow, а не «Moskva» и не «М.:», Saint Petersburg, а не «Sankt Peterburg» и не «SPb».

Название издательства/издателя. В отличие от места издания, название издательства для ссылок в References следует только транслитерировать (за исключением крайне редких случаев наличия у издателя параллельного официального англоязычного названия).

Примеры перевода русскоязычных источников литературы для англоязычного блока статьи

Книга:

Yuriev V.K., Moiseeva K.E., Glushchenko V.A. Fundamentals of public health and healthcare. Textbook. Saint Petersburg: SpetsLit; 2019. (In Russian).

Nikiforov O.N., ed. Saint Petersburg in 2021. Saint Petersburg: Petrostat; 2022. (In Russian).

Глава из книги:

Tutelyan V.A., Nikityuk D.B., Sharafetdinov Kh.Kh. Healthy nutrition is the basis of a healthy lifestyle and the prevention of chronic non-communicable diseases. In: Youth health: new challenges and prospects. T. 3. Moscow; 2019: 203–227. (In Russian).

Статья из журнала:

Karsanov A.M., Polunina N.V., Gogichaev T.K. Patient safety in surgery. Part 2: Quality management program for surgical treatment. Medical technologies. Evaluation and selection. 2019;1(35):56–65. DOI: 10.31556/2219-0678.2019.35.1.056-065. (In Russian).

Тезисы докладов, материалы научных конференций:

Markovskaya I.N., Zavyalova A.N., Kuznetsova Yu.V. Microbial landscape of a patient in the first year of life with dysphagia who has been in the ICU for a long time. XXX Congress of pediatric gastroenterologists of Russia and the CIS countries: abstract report. Moscow; 2023: 29–31.

Salov I.A., Marinushkin D.N. Obstetric tactics in intrauterine fetal death. In: Materialy IV Rossiyskogo foruma “Mat’ i ditya”. Part 1: Moscow; 2000: 516–519. (In Russian).

Авторефераты:

Avilov A.Yu. Deviations of gender role identity of men with mental retardation in a psychoneurological boarding school. PhD thesis. Saint Petersburg; 2021. (In Russian).

Описание интернет-ресурса:

Natural population movement. Moscow: Rosstat. Available at: <https://rosstat.gov.ru/folder/12781> (accessed: 10/23/2023). (In Russian).

Kealy M.A., Small R.E., Liamputtong P. Recovery after caesarean birth: a qualitative study of women’s accounts in Victoria,



Australia. BMC Pregnancy and Childbirth. 2010. Available at: <http://www.biomedcentral.com/1471-2393/10/47/> (accessed: 11.09.2013).

Пример списка литературы (References):

ЛИТЕРАТУРА

1. Криворученко В.К. Жестокое обращение с ребенком. Проявление и меры предотвращения. Информационный гуманитарный портал Знание. Понимание. Умение. 2012; 3. Доступен по: http://www.zpu-journal.ru/e-zpu/2012/3/Krivoruchenko_Child-Abuse (дата обращения: 27.12.2023).
2. Jacobi G., Dettmeyer R., Banaschak S., Brosig B., Herrmann B. Child abuse and neglect: diagnosis and management. Dtsch Arztebl Int. 2010;107(13):231-239. DOI: 10.3238/arztebl.2010.0231.

REFERENCES

1. Krivoruchenko V.K. Child abuse. Manifestation and prevention measures. Informationsnyy humanitarnyy portal Znaniye. Ponimaniye. Umeniye. 2012; 3. Available at: http://www.zpu-journal.ru/e-zpu/2012/3/Krivoruchenko_Child-Abuse (accessed: 27.12.2023) (In Russian).
2. Jacobi G., Dettmeyer R., Banaschak S., Brosig B., Herrmann B. Child abuse and neglect: diagnosis and management. Dtsch Arztebl Int. 2010;107(13):231-239. DOI: 10.3238/arztebl.2010.0231.

Для всех статей необходимо указывать индекс DOI в конце библиографического описания, а также EDN при его наличии.

Примеры:

Саттаров А.Э., Карелина Н.Р. Особенности ростовых процессов у мальчиков и юношей различных пропорций и телосложения, проживающих в южной части Кыргызстана. Педиатр. 2018;9(5):47–52. DOI: 10.17816/PED9547-52. EDN: YRAEPZ.

Voropaeva E.E., Khaidukova Yu.V., Kazachkova E.A., et al. Perinatal outcomes and morphological examination of placentas in pregnant women with critical lung lesions in new COVID-19 coronavirus infection. Ural Medical Journal. 2023;22(2):109–121. DOI: 10.52420/2071-5943-2023-22-2-109-121. EDN: CXRCMN. (In Russian).

ОТВЕТСТВЕННОСТЬ ЗА ПРАВИЛЬНОСТЬ БИБЛИОГРАФИЧЕСКИХ ДАННЫХ НЕСЕТ АВТОР.

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Редакция отбирает, готовит к публикации и публикует переданные Авторами материалы. Авторское право на конкретную статью принадлежит авторам статьи. Авторский гонорар за публикации статей в Журнале не выплачивается. Автор передает, а Редакция принимает авторские материалы на следующих условиях:

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Заключением Договора со стороны Редакции является опубликование рукописи данного Автора в журнале «Russian Biomedical Research» и размещение его текста в сети Интернет. Заключением Договора со стороны Автора, т.е. полным и безоговорочным принятием Автором условий Договора, является передача Автором рукописи и экспертного заключения.

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Сайты журнала: http://www.gpmu.org/science/pediatrics-magazine/Russian_Biomedical_Research, <https://ojs3.gpmu.org/index.php/biomedical-research>

ИЗДАТЕЛЬСТВО ПЕДИАТРИЧЕСКОГО УНИВЕРСИТЕТА ПРЕДСТАВЛЯЕТ

ОРТОПЕДИЧЕСКАЯ СТОМАТОЛОГИЯ. ПРОТЕЗИРОВАНИЕ НЕСЪЁМНЫМИ КОНСТРУКЦИЯМИ ЗУБНЫХ ПРОТЕЗОВ

М. Ф. Сухарев, С. Б. Фицев, М. Г. Рожкова



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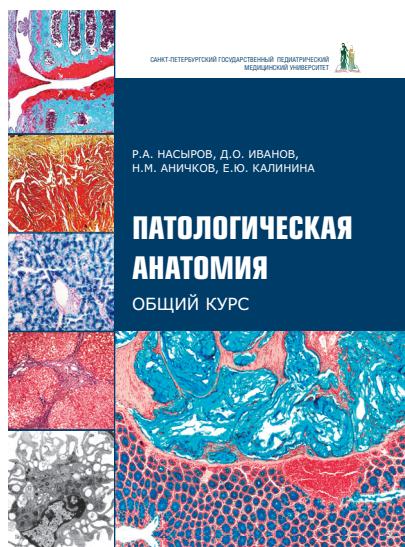
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Р.А. Насыров, Д.О. Иванов, Н.М. Аничков, Е.Ю. Калинина



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