Review
UDC 159.944.4+612.4+599.32/.324+615.357
https://doi.org/10.56871/RBR.2025.83.69.004

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

Sarng S. Pyurveev[1, 2], Alesia S. Oskina[1], Sofia V. Ulanova[1]

[1] Saint Petersburg State Pediatric Medical University, 2 Litovskaya str., Saint Petersburg, 194100, Russian Federation
[2] Institute of Experimental Medicine, 12 Akademika Pavlova str., Saint Petersburg, 197022, Russian Federation

For citation: Pyurveev S.S., Oskina A.S., Ulanova S.V. Translational animal models in the study of stress response regulation and complex mechanisms of glucocorticoid action. *Russian Biomedical Research.* 2025;10(4):58–83. https://doi.org/10.56871/RBR.2025.83.69.004.

Received: 29.08.2025 **Revised: 20.10.2025** **Accepted: 15.12.2025**

Corresponding author:
Sarng S. Purveev
E-mail:
dr.purveev@gmail.com

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 adrenocorticotropic 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 mineralcorticoid 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

Funding. This study was not supported by any external sources of funding.

Обзор

https://doi.org/10.56871/RBR.2025.83.69.004

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

Сарнг Саналович Пюрвеев[1, 2], Алеся Сергеевна Оськина[1], София Владимировна Уланова[1]

[1] Санкт-Петербургский государственный педиатрический медицинский университет, 194100, г. Санкт-Петербург, ул. Литовская, д. 2, Российская Федерация
[2] Институт экспериментальной медицины, 197022, г. Санкт-Петербург, ул. Академика Павлова, д. 12, Российская Федерация

Для цитирования: Пюрвеев С.С., Оськина А.С., Уланова С.В. Трансляционные модели на животных в исследовании регуляции стрессового ответа и сложных механизмов действия глюкокортикоидов. *Российские биомедицинские исследования*. 2025;10(4):58–83. https://doi.org/10.56871/RBR.2025.83.69.004.

Поступила: 29.08.2025 **Одобрена: 20.10.2025** **Принята к печати: 15.12.2025**

Автор для корреспонденции:
Сарнг Саналович Пюрвеев
E-mail:
dr.purveev@gmail.com

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

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

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 adrenocorticotropic 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, adrenocorticotropic 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 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 suprachiasmatic 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 suprachiasmatic 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].

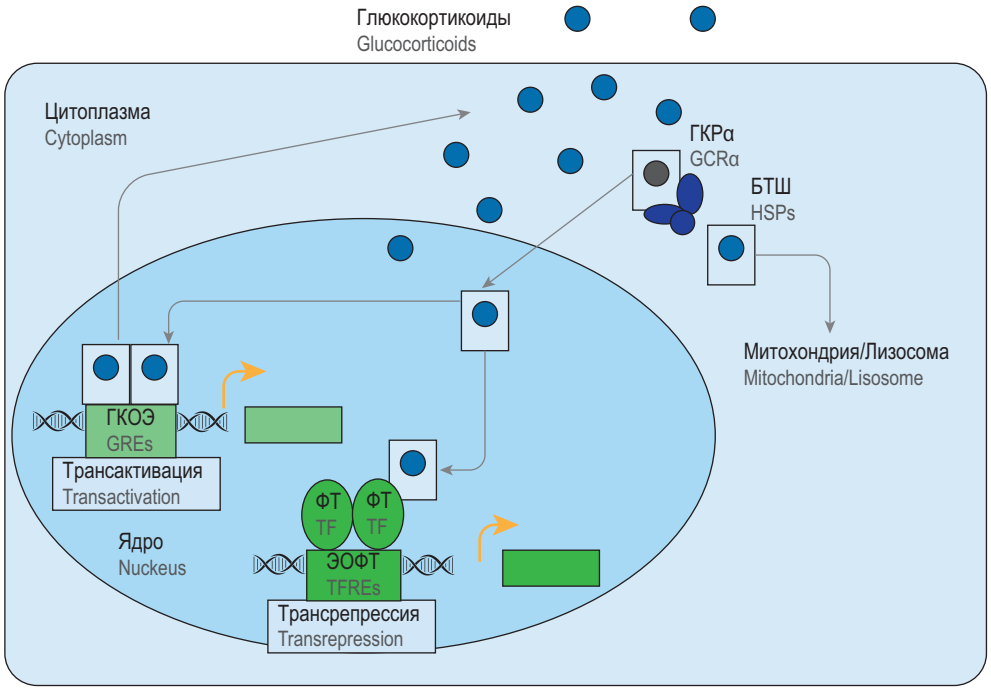

Fig. 1. **Intracellular circulation of glucocorticoid receptors. The circulation of glucocorticoid receptors between the cytoplasm and the nucleus and the regulation of transcription of genes sensitive to glucocorticoids. Glucocorticoid receptors are further translocated into mitochondria or lysosomes [36]. HSPs — heat shock proteins; GCRα — 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; ГКРα — 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 can 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-κB/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 TNFα injection. Thus, IL-1 receptor levels in the hippocampus are relatively resistant to modulation by circulating GCs, whereas TNFα 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, GRα and GRβ, were identified [61]. GRα binds cortisol with high affinity and is transcriptionally active, whereas GRβ does not bind cortisol and lacks the same transactivation properties. GRβ has also been shown to inhibit the activity of zebrafish GRα, 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

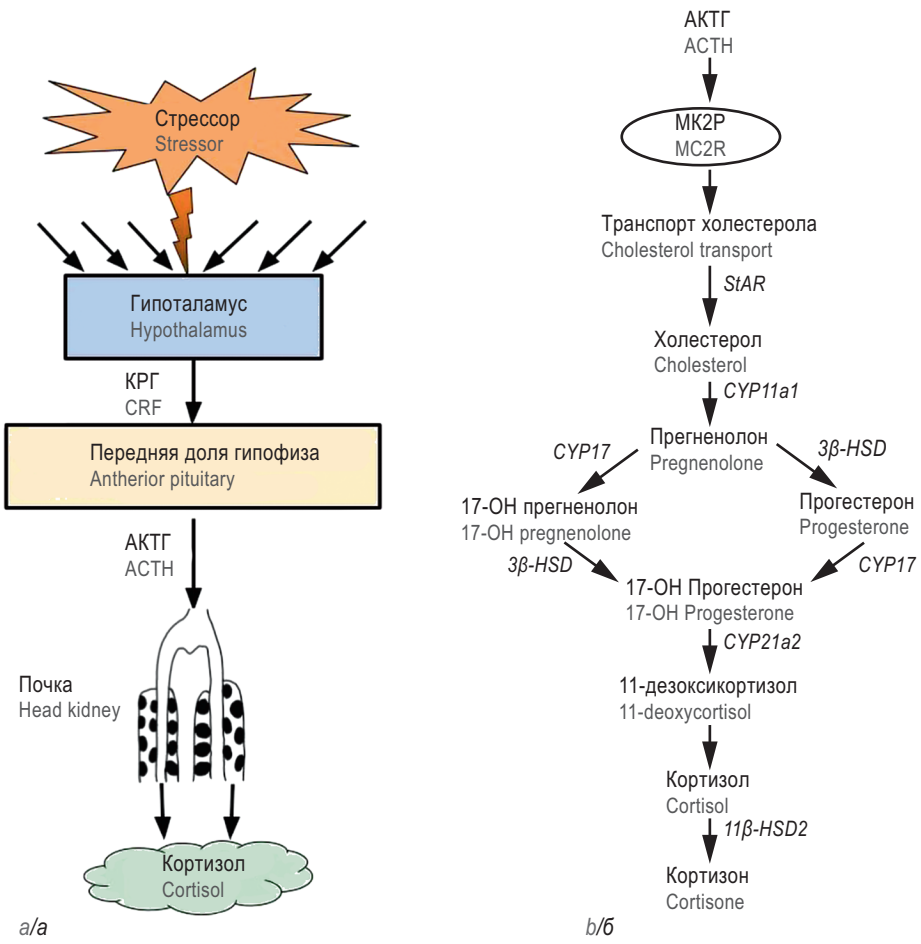

Fig. 2. **Scheme of the HPA axis and cortisol synthesis: *a* — schematic representation of the hypothalamic-pituitary-adrenal axis and signaling cascade; *b* — cortisol synthesis in the interrenal cells is stimulated by the binding of ACTH to MC2R. MC2R — melanocortin-2 receptors; StAR — steroidogenic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

Рис. 2. Схема строения ГГН-оси и синтеза кортизола: *а* — 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 (P450scc), 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 metabolism 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 11β-HSD2, an enzyme that metabolizes into cortisone. However, between 1.5 and 25 hours post-fertilization, very few 11β-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.

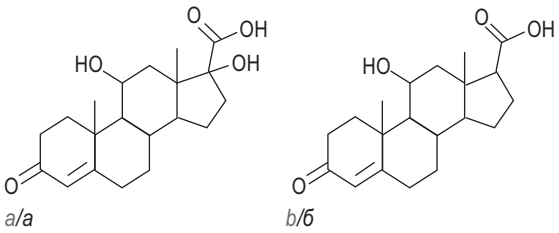

Fig. 3. **Biochemical structure of cortisol (*a*) and corticosterone (*b*) (drawing by the authors)**

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].

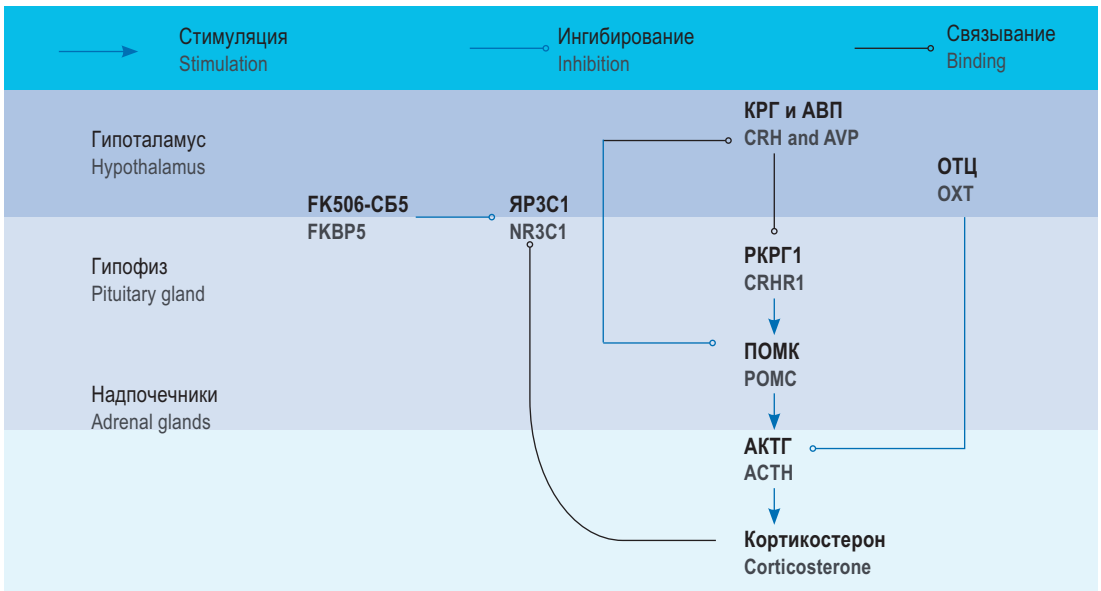

Fig. 4. **Scheme of hypothalamic-pituitary-adrenal axis regulation in rats. AVP — corticotropin releasing hormone and arginine vasopressin; ACTH — adrenocorticotropin hormone; CRH — corticotropin releasing hormone; OXT — oxytocin; POMC — proopiomelanocortin; CRHR1 — CRH receptor; NR3C1 — nuclear glucocorticoid 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-рилизинг гормон; ОТЦ — окситоцин; ПОМК — проопиомеланокортин; РКРГ1 — рецептор к кортикотропин-релизинг гормону 1; ЯР3-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 adrenocorticotropic 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, GRα and GRβ [77, 85, 88]. GRβ does not bind classical agonists such as cortisol or dexamethasone, acts as a negative inhibitor of GRα, and is involved in various immune-related responses. The GRβ variant has not been detected in animal model species to date, such as rats and mice. However, a GRβ 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-1β and IL-6), brain-derived neurotrophic factor (BDNF), gamma interferon (IFN-γ), and tumor necrosis factor-alpha (TNFα), 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 behavior, 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

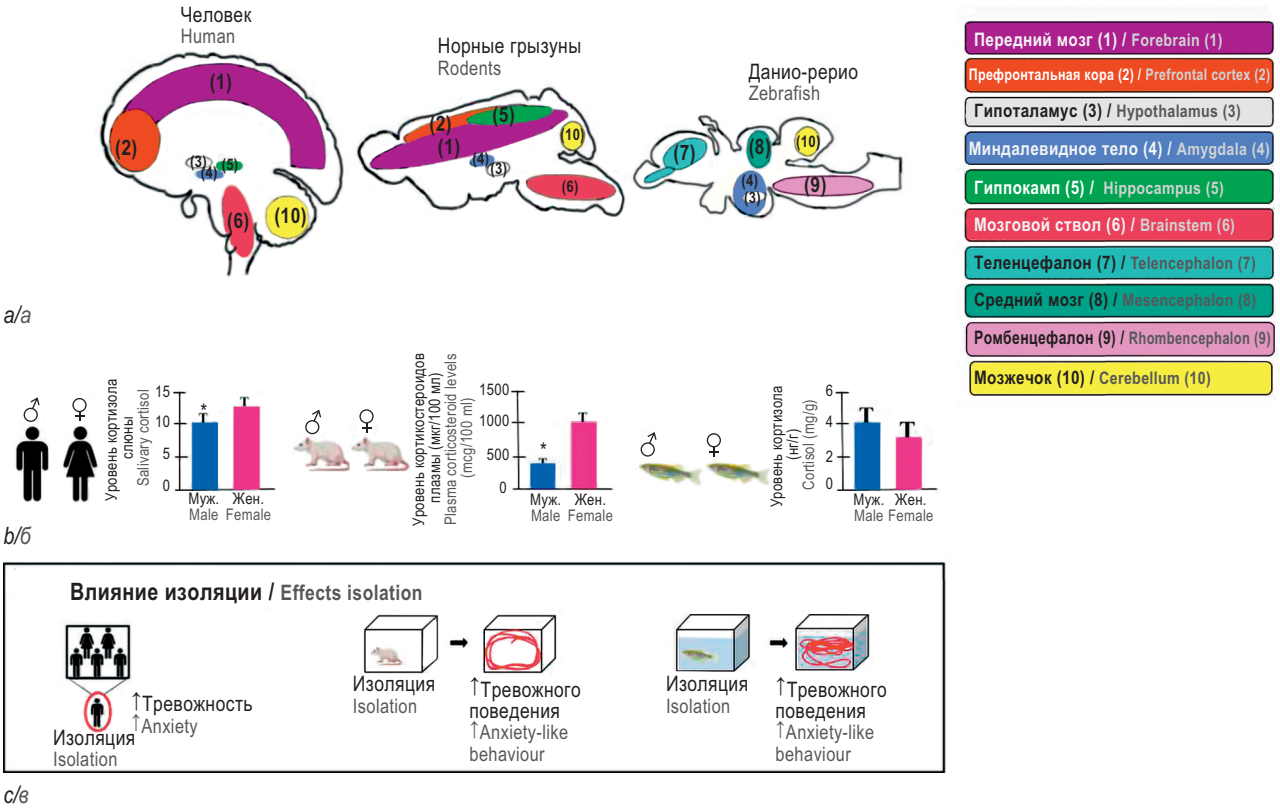

Fig. 5. **Comparison of stress status in humans, burrowing rodents and zebrafish: *a* — comparison of the location of the main structures of the brain; *b* — changes in cortisol levels in response to stress depending on gender; *c* — evaluation of behavioral effectiveness (adapted from [163])**

Рис. 5. Сравнение реакции на стресс у человека, норных грызунов и Данио-рерио: *а* — 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)
		• Signal transduction in response to peaks in corticosterone release depends on the dynamic interaction of the glucocorticoid receptor and the mineralocorticoid receptor [114]
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 ГРα (классический) и ГРβ, ГРγ. The mammalian genome contains a single glucocorticoid receptor gene. However, alternative splicing produces glucocorticoid receptor isoforms GRα (classical) and GRβ, GRγ.
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 *in vivo* 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 *in vivo* 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 — adrenocorticotropic hormone; GR — glucocorticoid receptor; CRH — corticotropin-releasing hormone.

Примечание: АКТГ — адренокортикотропный 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).

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.

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).

ЛИТЕРАТУРА / REFERENCES

1. Odaka H., Adachi N., Numakawa T. Impact of glucocorticoid on neurogenesis. *Neural Regen Res*. 2017;12(7):1028–1035. https://doi.org/10.4103/1673-5374.211174.
2. Gulyaeva N.V. Glucocorticoids orchestrate adult hippocampal plasticity: growth points and translational aspects. *Biochemistry (Moscow)*. 2023;88:565–589. https://doi.org/10.1134/S0006297923050012. EDN: CMIINV.
3. Batchelor V., Pang T.Y. HPA axis regulation and stress response is subject to intergenerational modification by paternal trauma and stress. *Gen Comp Endocrinol*. 2019;280:47–53. https://doi.org/10.1016/j.ygcen.2019.04.010.
4. Bassil K., Krontira A.C., Leroy T. et al. *In vitro* modeling of the neurobiological effects of glucocorticoids: A review. *Neurobiol stress*. 2023:23:100530. https://doi.org/10.1016/j.ynstr.2023.100530. EDN: XSCZFT.
5. Loi M., Mossink J.C., Meerhoff G.F. et al. Effects of early-life stress on cognitive function and hippocampal structure in female rodents. *Neuroscience*. 2017:342:101–119. https://doi.org/10.1016/j.neuroscience.2015.08.024.
6. Балакина М.Е., Дегтярева Е.В., Некрасов М.С., и др. Воздействие раннего постнатального стресса на психоэмоциональное состояние и развитие склонности к чрезмерному употреблению высокоуглеводной пищи у крыс. *Российские биомедицинские исследования*. 2021;6(2):27–37. EDN: ABECPH.
Balakina M.E., Degtyareva E.V., Nekrasov M.S., Brus T.V., Purveev S.S. Effect of early postnatal stress upon psychoemotional state and development of excessive consumption of high-carbohydrate food in rats. *Russian Biomedical Research*. 2021;6(2):27–37. (In Russian). EDN: ABECPH.
7. Podgorny O.V., Gulyaeva N.V. Glucocorticoid-mediated mechanisms of hippocampal damage: Contribution of subgranular neurogenesis. *J Neurochem*. 2021;157(3):370–392. https://doi.org/10.1111/jnc.15265. EDN: JVEVPZ.
8. Vazquez D.M. Stress and the developing limbic-hypothalamic-pituitary-adrenal axis. *Psychoneuroendocrinol*. 1998;23(7):663–700. https://doi.org/10.1016/s0306-4530(98)00029-8.

9. Wang Q., Verweij E.W.E., Krugers H.J., et al. Distribution of the glucocorticoid receptor in the human amygdala; changes in mood disorder patients. *Brain Struct Funct*. 2014;219(5):1615–1626. https://doi.org/10.1007/s00429-013-0589-4. EDN: UUABSF.
10. Numakawa T., Odaka H., Adachi N. Actions of brain-derived neurotrophic factor and glucocorticoid stress in neurogenesis. *Int J Mol Sci*. 2017;18(11):2312. https://doi.org/10.3390/ijms18112312.
11. McEwen B.S., Nasca C., Gray J.D. Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. *Neuropsychopharmacology*. 2016;41(1):3–23. https://doi.org/10.1038/npp.2015.171.
12. Miller W.L. The hypothalamic-pituitary-adrenal axis: a brief history. *Horm Res Paediatr*. 2018;89(4):212–223. https://doi.org/10.1159/000487755.
13. Spiga F., Walker J.J., Terry J.R., Lightman S.L. HPA axis-rhythms. *Compr Physiol*. 2014;4(3):1273–1298. https://doi.org/10.1002/cphy.c140003.
14. Leistner C., Menke A. Hypothalamic-pituitary-adrenal axis and stress. *Handb Clin Neurol*. 2020;175:55–64. https://doi.org/10.1016/B978-0-444-64123-6.00004-7.
15. Sheng J.A., Bales N.J., Myers S.A. et al. The hypothalamic-pituitary-adrenal axis: development, programming actions of hormones, and maternal-fetal interactions. *Front Behav Neurosci*. 2021;14:601939. https://doi.org/10.3389/fnbeh.2020.601939.
16. Nicolaides N.C., Charmandari E., Chrousos G.P., Kino T. Circadian endocrine rhythms: the hypothalamic-pituitary-adrenal axis and its actions. *Ann N Y Acad Sci*. 2014;1318(1);71–80. https://doi.org/10.1111/nyas.12464. EDN: UVYHXJ.
17. Kinlein S.A., Karatsoreos I.N. The hypothalamic-pituitary-adrenal axis as a substrate for stress resilience: Interactions with the circadian clock. *Front Neuroendocrinol*. 2020;56:100819. https://doi.org/10.1016/j.yfrne.2019.100819. EDN: KOUZZH.
18. Busada J.T., Cidlowski J.A. Mechanisms of glucocorticoid action during development. Curr Top Dev Biol. 2017;125:147–170. https://doi.org/10.1016/bs.ctdb.2016.12.004.
19. Chetty S., Friedman A.R., Taravosh-Lahn K. et al. Stress and glucocorticoids promote oligodendrogenesis in the adult hippocampus. *Mol Psychiatry*. 2014;19(12):1275–1283. https://doi.org/10.1038/mp.2013.190.
20. Russell G., Lightman S. The human stress response. *Nat Rev Endocrinol*. 2019;15(9):525–534. https://doi.org/10.1038/s41574-019-0228-0.
21. Choi G.E., Chae C.W., Park M.R. et al. Prenatal glucocorticoid exposure selectively impairs neuroligin 1-dependent neurogenesis by suppressing astrocytic FGF2-neuronal FGFR1 axis. *Cell Mol Life Sci*. 2022;79(6):294. https://doi.org/10.1007/s00018-022-04313-2. EDN: FTOKVO.
22. Lehmann M.L., Brachman R.A., Martinowich K., Schloesser R.J., Herkenham M. Glucocorticoids orchestrate divergent effects on mood through adult neurogenesis. *J Neurosci*. 2013;33(7):2961–2972. https://doi.org/10.1523/JNEUROSCI.3878-12.2013.
23. Van Looveren K., Van Boxelaere M., Callaerts-Vegh Z., Libert C. Cognitive dysfunction in mice lacking proper glucocorticoid receptor dimerization. *PLoS One*. 2019;14(12):e0226753. https://doi.org/10.1371/journal.pone.0226753. EDN: QUCKLF.
24. Бычков Е.Р., Карпова И.В., Цикунов С.Г. и др. Действие острого психического стресса на обмен моноаминов в мезокортикальной и нигростриатной системах головного мозга крыс. *Педиатр*. 2021;12(6):35–42. https://doi.org/10.17816/PED12635-42. EDN: VFATQN.
Bychkov E.R., Karpova I.V., Tsikunov S.G., Krytskaya D.V., Lebedev A.A., Tissen I.Y., Pyurveev S.S., Shabanov P.D. The effect of acute mental stress on the exchange of monoamines in the mesocortical and nigrostriatal systems of the rat brain. *Pediatrician (St. Petersburg)*. 2021;12(6):35–42. 2021;12(6):35–42. (In Russian). https://doi.org/10.17816/PED12635-42. EDN: VFATQN.
25. Scherholz M.L., Schlesinger N., Androulakis I.P. Chronopharmacology of glucocorticoids. *Adv Drug Deliv Rev*. 2019;151–152:245–261. https://doi.org/10.1016/j.addr.2019.02.004.
26. Hörberg J., Moreau K., Tamas M.J., Reymer A. Sequence-specific dynamics of DNA response elements and their flanking sites regulate the recognition by AP-1 transcription factors. *Nucleic Acids Res*. 2021;49(16):9280–9293. https://doi.org/10.1093/nar/gkab691. EDN: JGUWWD.
27. Amaya J.M., Viho E.M.G, Sips H.C.M. et al. Gene expression changes in the brain of a Cushing's syndrome mouse model. *J Neuroendocrinol*. 2022;34(4):e13125. https://doi.org/10.1111/jne.13125.
28. Pariante C.M., Lightman S.L. The HPA axis in major depression: classical theories and new developments. *Trends Neurosci*. 2008;31(9):464–468. https://doi.org/10.1016/j.tins.2008.06.006.
29. Planchez B., Surget A., Belzung C. Animal models of major depression: drawbacks and challenges. *J Neural Transm*. 2019;126(11):1383–1408. https://doi.org/10.1007/s00702-019-02084-y. EDN: RFKNQL
30. Большаков А.П., Третьякова Л.В., Квичанский А.А., Гуляева Н.В. Глюкокортикоиды в нейровоспалении гиппокампа: доктор Джекилл и мистер Хайд. *Биохимия*. 2021;86(2):186–199. https://doi.org/10.31857/S0320972521020044. EDN: KAKHFC.
Bolshakov A.P., Tretyakova L.V., Kvichansky A.A., Gulyaeva N.V. Glucocorticoids in hippocampal neuroinflammation: Dr. Jekyll and Mr. Hyde. *Biochemistry (Moscow)*. 2021;86(2):186–199. (In Russian). https://doi.org/10.31857/S0320972521020044. EDN: KAKHFC.
31. Makara G.B., Haller J. Non-genomic effects of glucocorticoids in the neural system. Evidence, mechanisms and implications. *Progr Neurobiol*. 2001;65(4):367–390. https://doi.org/10.1016/s0301-0082(01)00012-0.
32. Perry R.J., Resch J.M., Douglass A.M. et al. Leptin's hunger-suppressing effects are mediated by the hypothalamic-pituitary-adrenocortical axis in rodents. *Proc Natl Acad Sci U S A*. 2019;116(27):13670–13679. EDN: ZFDZAE https://doi.org/10.1073/pnas.1901795116.
33. Oomen C.A., Girardi C.E., Cahyadi R. et al. Opposite effects of early maternal deprivation on neurogenesis in male versus female rats. *PLoS One*. 2009;4(1):e3675. https://doi.org/10.1371/journal.pone.0003675.

34. Betancur C., Borrell J., Guaza C. Cytokine regulation of corticosteroid receptors in the rat hippocampus: effects of interleukin-1, interleukin-6, tumor necrosis factor and lipopolysaccharide. *Neuroendocrinology*. 1995;62(1):47–54. https://doi.org/10.1159/000126987.
35. Viho E.M.G, Buurstede J.C., Berkhout J.B. et al. Cell type specificity of glucocorticoid signaling in the adult mouse hippocampus. *J Neuroendocrinol*. 2022;34(2):e13072. https://doi.org/10.1111/jne.13072. EDN: UXZDMS.
36. Juszczak G.R., Stankiewicz A.M. Glucocorticoids, genes and brain function. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;82:136–168. https://doi.org/10.1016/j.pnpbp.2017.11.020. EDN: YEAXID.
37. Sanguino-Gómez J., Krugers H.J. Early-life stress impairs acquisition and retrieval of fear memories: sex-effects, corticosterone modulation, and partial prevention by targeting glucocorticoid receptors at adolescent age. *Neurobiol Stress*. 2024;31:100636. https://doi.org/10.1016/j.ynstr.2024.100636. EDN: SQPTJU.
38. Mourtzi N., Sertedaki A., Charmandari E. Glucocorticoid signaling and epigenetic alterations in stress-related disorders. *Int J Mol Sci*. 2021;22(11):5964. https://doi.org/10.3390/ijms22115964. EDN: GLZQQT.
39. Churilov A.N., Milton J.G. Modeling pulsativity in the hypothalamic-pituitary-adrenal hormonal axis. *Sci Rep*. 2022;12(1):8480. https://doi.org/10.1038/s41598-022-12513-w. EDN: TGOJIC.
40. Grillo C.A., Piroli G.G., Wood G.E. et al. Immunocytochemical analysis of synaptic proteins provides new insights into diabetes-mediated plasticity in the rat hippocampus. *Neuroscience*. 2005;136(2):477–486. https://doi.org/10.1016/j.neuroscience.2005.08.019.
41. Wiechmann T., Röh S., Sauer S. et al. Identification of dynamic glucocorticoid-induced methylation changes at the FKBP5 locus. *Clinical Epigenetics*. 2019;11(1):83. https://doi.org/10.1186/s13148-019-0682-5. EDN: XAPBNE.
42. Thomassin H., Flavin M., Espinás M.L. et al. Glucocorticoid-induced DNA demethylation and gene memory during development. *EMBO J*. 2001;20(8):1974–1983. https://doi.org/10.1093/emboj/20.8.1974.
43. Zanta N.C., Assad N., Suchecki D. Neurobiological mechanisms involved in maternal deprivation-induced behaviours relevant to psychiatric disorders. *Front Mol Neurosci*. 2023;16:1099284. https://doi.org/10.3389/fnmol.2023.1099284. EDN: IHKULP.
44. Snyder J.S., Soumier A., Brewer M. et al. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature*. 2011;476(7361):458–461. https://doi.org/10.1038/nature10287.
45. Erdmann G., Berger S., Schütz G. Genetic dissection of glucocorticoid receptor function in the mouse brain. *J Neuroendocrinol*. 2008;20(6):655–659. https://doi.org/10.1111/j.1365-2826.2008.01717.x.
46. Rentesi G., Antoniou K., Marselos M. et al. Early maternal deprivation-induced modifications in the neurobiological, neurochemical and behavioral profile of adult rats. *Behav Brain Res*. 2013;244:29–37. https://doi.org/10.1016/j.bbr.2013.01.040.
47. Masana M., Westerholz S., Kretzschmar A. et al. Expression and glucocorticoid-dependent regulation of the stress-inducible protein DRR1 in the mouse adult brain. *Brain Struct Funct*. 2018;223(9):4039–4052. https://doi.org/10.1007/s00429-018-1737-7. EDN: GGVGBE.
48. Noorlander C.W., Tijsseling D., Hessel E.V. et al. Antenatal glucocorticoid treatment affects hippocampal development in mice. *PLoS One*. 2014;9(1):e85671. https://doi.org/10.1371/journal.pone.0085671.
49. Morais M., Santos P.A., Mateus-Pinheiro A. et al. The effects of chronic stress on hippocampal adult neurogenesis and dendritic plasticity are reversed by selective MAO-A inhibition. *J Psychopharmacol*. 2014;28(12):1178–1183. https://doi.org/10.1177/0269881114553646.
50. Nishi M., Horii-Hayashi N., Sasagawa T., Matsunaga W. Effects of early life stress on brain activity: implications from maternal separation model in rodents. *Gen Comp Endocrinol*. 2013;181:306–309. https://doi.org/10.1016/j.ygcen.2012.09.024.
51. Hernandez M., Ghislin S., Lalonde R., Strazielle C. Corticosterone effects on postnatal cerebellar development in mice. *Neurochem Int*. 2023;171:105611. https://doi.org/10.1016/j.neuint.2023.105611. EDN: VHOYJK.
52. Тодосенко Н.М., Королева Ю.А., Хазиахматова О.Г., Юрова К.А., Литвинова Л.С. Геномные и негеномные эффекты глюкокортикоидов. *Гены и клетки*. 2017;12(1):27–33. https://doi.org/10.23868/201703003.
Todosenko N.M., Yu.A. Koroleva, Khaziakhmatova O.G., Yurova K.A., Litvinova L.S. Genomic and non-genomic effects of glucocorticoids. *Genes and Cells*. 2017;12(1):27–33. (In Russian). https://doi.org/10.23868/201703003.
53. Ferreira A.C., Marques F. The Effects of stress on hippocampal neurogenesis and behavior in the absence of lipocalin-2. *Int J Mol Sci*. 2023;24(21):15537. https://doi.org/10.3390/ijms242115537. EDN: PNBIFA.
54. Шабанов П.Д., Якушина Н.Д., Лебедев А.А. Фармакология пептидных механизмов игрового поведения у крыс. *Вопросы наркологии*. 2020;4(187):24–44. https://doi.org/10.47877/0234-0623_2020_4_24. EDN: JBUQJN.
Shabanov P.D., Yakushina N.D., Lebedev A.A. Pharmacology of peptide mechanisms of gambling behavior in rats. *Journal of Addiction Problems*. 2020;4(187):24–44. (In Russian). https://doi.org/10.47877/0234-0623_2020_4_24. EDN: JBUQJN.
55. Spencer R.L., Deak T. A users guide to HPA axis research. *Physiol Behav*. 2017;178:43–65. https://doi.org/10.1016/j.physbeh.2016.11.014.
56. Онуфриев М.В., Моисеева Ю.В., Гуляева Н.В. Моделирование гиперкортикостеронемии у крыс с помощью осмотических насосов. *Российский физиологический журнал им. И.М. Сеченова*. 2022;108(11):1542–1550. https://doi.org/10.31857/S0869813922110085. EDN: ABNXYC.
Onufriev M.V., Moiseeva Yu.V., Gulyaevaa N.V. Modeling hypercorticosteronemia in rats using osmotic pumps.

Rossiyskiy fiziologicheskiy zhurnal im. I.M. Sechenova. 2022;108(11):1542–1550. (In Russian). https://doi.org/10.31857/S0869813922110085. EDN: ABNXYC.
57. Silverman M.N., Sternberg E.M. Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. *Ann N Y Acad Sci*. 2012;1261:55–63. https://doi.org/10.1111/j.1749-6632.2012.06633.x.
58. Merkulov V.M., Merkulova T.I., Bondar N.P. Mechanisms of brain glucocorticoid resistance in stress-induced psychopathologies. *Biochemistry (Moscow)*. 2017;82(3):351–365. https://doi.org/10.1134/S0006297917030142. EDN: YVDPIX.
59. Joëls M., de Kloet E.R. 30 years of the mineralocorticoid receptor: The brain mineralocorticoid receptor: A saga in three episodes. *J Endocrinol*. 2017;234(1):49–66. https://doi.org/10.1530/JOE-16-0660.
60. Peles G., Swaminathan A., Levkowitz G. Glucocorticoid-sensitive period of corticotroph development-Implications for mechanisms of early life stress. *J Neuroendocrinol*. 2023;35(11):e13229. https://doi.org/10.1111/jne.13229. EDN: IUXTUQ.
61. Chatzopoulou Chatzi A. Unraveling the glucocorticoid receptor pathway in zebrafish [dissertation]. Institute of Biology, Faculty of Science, Leiden University; 2012.
62. Dinarello A., Licciardello G., Fontana C.M., et al. Glucocorticoid receptor activities in the zebrafish model: a review. *J Endocrinol*. 2020;247(3):63–82. https://doi.org/10.1530/JOE-20-0173. EDN: QUGIEI.
63. Faught E., Schaaf M.J.M. Molecular mechanisms of the stress-induced regulation of the inflammatory response in fish. *Gen Comp Endocrinol*. 2024;345:114387. https://doi.org/10.1016/j.ygcen.2023.114387. EDN: HSOZMV.
64. Reyes-Contreras M., Glauser G., Rennison D.J., Taborsky B. Early-life manipulation of cortisol and its receptor alters stress axis programming and social competence. *Philos Trans R Soc Lond B Biol Sci*. 2019;374(1770):20180119. https://doi.org/10.1098/rstb.2018.0119.
65. Alsop D., Vijayan M. The zebrafish stress axis: molecular fallout from the teleost-specific genome duplication event. *Gen Comp Endocrinol*. 2009;161(1):62–66. https://doi.org/10.1016/j.ygcen.2008.09.011.
66. Alsop D., Vijayan M.M. Molecular programming of the corticosteroid stress axis during zebrafish development. *Comp Biochem Physiol A Mol Integr Physiol*. 2009;153(1):49–54. https://doi.org/10.1016/j.cbpa.2008.12.008.
67. Eachus H., Ryu S., Placzek M., Wood J. Zebrafish as a model to investigate the CRH axis and interactions with DISC1. *Curr Opin Endocr Metab Res*. 2022;26;100383. https://doi.org/10.1016/j.coemr.2022.10038. EDN: AQATXV.
68. Eachus H., Choi M.K., Ryu S. The effects of early life stress on the brain and behaviour: insights from zebrafish models. *Front Cell Dev Biol*. 2021;9:657591. https://doi.org/10.3389/fcell.2021.657591. EDN: CUPFLD.
69. Lee H.B., Shams S., Dang Thi V.H. et al. Key HPI axis receptors facilitate light adaptive behavior in larval zebrafish. *Sci Rep*. 2024;14(1):7759. https://doi.org/10.1038/s41598-024-57707-6. EDN: ISMOKI.
70. Buenhombre J., Daza-Cardona E.A., Sousa P., Gouveia A. Jr. Different influences of anxiety models, environmental enrichment, standard conditions and intraspecies variation (sex, personality and strain) on stress and quality of life in adult and juvenile zebrafish: A systematic review. *Neurosci Biobehav Rev.* 2021;131:765–791. https://doi.org/10.1016/j.neubiorev.2021.09.047. EDN: EMYEDZ.
71. Alsop D., Vijayan M.M. Development of the corticosteroid stress axis and receptor expression in zebrafish. *Am J Physiol Regul Integr Comp Physiol*. 2008;294(3):711–719. https://doi.org/10.1152/ajpregu.00671.2007. EDN: MLLNKR.
72. Blanco I., Conant K. Extracellular matrix remodeling with stress and depression: Studies in human, rodent and zebrafish models. *Eur J Neurosci*. 2021;53(12):3879–3888. https://doi.org/10.1111/ejn.14910. EDN: NKCCNU.
73. Andersen-Civil A.I.S, Sawal R.A., Vanwalleghem G.C. Zebrafish (Danio rerio) as a translational model for neuro-immune interactions in the enteric nervous system in autism spectrum disorders. *Brain Beh Immun*. 2023;112:254–266. https://doi.org/10.1016/j.bbi.2023.06.001. EDN: MZSRWX.
74. Gallas-Lopes M., Bastos L.M., Benvenutti R. et al. Systematic review and meta-analysis of 10 years of unpredictable chronic stress in zebrafish. *Lab Animal*. 2023;52(10):229–246. https://doi.org/10.1038/s41684-023-01239-5. EDN: JNCLDX.
75. Kwong R.W., Kumai Y., Perry S.F. The physiology of fish at low pH: the zebrafish as a model system. *J Exp Biol*. 2014;217(5):651–662. https://doi.org/10.1242/jeb.091603.
76. Fonseka T.M., Wen X.Y., Foster J.A., Kennedy S.H. Zebrafish models of major depressive disorders. *J Neurosci Res*. 2016;94(1):3–14. https://doi.org/10.1002/jnr.23639. EDN: XPFXYT.
77. Al-Zoubi R.M., Abu-Hijleh H., Zarour A. et al. Zebrafish model in illuminating the complexities of post-traumatic stress disorders: a unique research tool. *Int J Mol Sci*. 2024;25(9):4895. https://doi.org/10.3390/ijms25094895. EDN: DOLQGY.
78. Gilmour K.M., Bard B. Social buffering of the stress response: insights from fishes. *Biol Lett*. 2022;18(10):20220332. https://doi.org/10.1098/rsbl.2022.0332. EDN: GJZNNT.
79. Schaaf M.J., Chatzopoulou A., Spaink H.P. The zebrafish as a model system for glucocorticoid receptor research. *Comp Biochem Physiol A Mol Integr Physiol*. 2009;153(1):75–82. https://doi.org/10.1016/j.cbpa.2008.12.014.
80. Hillegass J.M., Villano C.M., Cooper K.R., White L.A. Matrix metalloproteinase-13 is required for zebrafish (Danio rerio) development and is a target for glucocorticoids. *Toxicol Sci*. 2007;100(1):168–179. https://doi.org/10.1093/toxsci/kfm192.
81. Mommsen T.P., Vijayan M.M., Moon T.W. Cortisol in teleosts: dynamics, mechanisms of action, and metabolic regulation. *Reviews in Fish Biology and Fisheries*. 1999;9(3):211–268. https://doi.org/10.1023/A:1008924418720. EDN: YCTXGX.
82. Aluru N., Vijayan M.M. Hepatic transcriptome response to glucocorticoid receptor activation in rainbow trout. *Physiol Genomics*. 2007;31(3):483–491. https://doi.org/10.1152/physiolgenomics.00118.2007. EDN: MKINMJ.

83. Nica G., Herzog W., Sonntag C., Hammerschmidt M. Zebrafish pit1 mutants lack three pituitary cell types and develop severe dwarfism. *Mol Endocrinol*. 2004;18(5):1196–1209. https://doi.org/10.1210/me.2003-0377.
84. Keller P.J., Schmidt A.D., Wittbrodt J., Stelzer E.H. Reconstruction of zebrafish early embryonic development by scanned light sheet microscopy. *Science*. 2008;322(5904):1065–1069. https://doi.org/10.1126/science.1162493.
85. Lieschke G.J., Currie P.D. Animal models of human disease: zebrafish swim into view. *Nat Rev Genet*. 2007;8(5):353–367. https://doi.org/10.1038/nrg2091. EDN: MMAWCV.
86. Barrett R., Chappell C., Quick M. et al. A rapid, high content, in vivo model of glucocorticoid-induced osteoporosis. *Biotechnol J*. 2006;1(6):651–655. https://doi.org/10.1002/biot.200600043.
87. Schaaf M.J., Champagne D., van Laanen I.H. et al. Discovery of a functional glucocorticoid receptor beta-isoform in zebrafish. *Endocrinology*. 2008;149(4):1591–1599. https://doi.org/10.1210/en.2007-1364.
88. Kachanov D., Elistratov L., Guseinov H. et al. A comparative review of the use of danio rerio (zebrafish) as a model object in preclinical studies. *Georgian Med News*. 2023;(337):21–24.
89. Steenbergen P.J., Richardson M.K., Champagne D.L. The use of the zebrafish model in stress research. *Prog Neuropsychopharmacol Biol Psychiatry*. 2001;35(6):1432–1451. https://doi.org/10.1016/j.pnpbp.2010.10.010. EDN: PHMLEP.
90. Shen C., Zuo Z. Zebrafish (Danio rerio) as an excellent vertebrate model for the development, reproductive, cardiovascular, and neural and ocular development toxicity study of hazardous chemicals. *Environ Sci Pollut Res Int*. 2020;27(35):43599–43614. https://doi.org/10.1007/s11356-020-10800-5. EDN: GSWWRN.
91. Joëls M., Karst H., Sarabdjitsingh R.A. The stressed brain of humans and rodents. *Acta Physiol*. 2018;223(2):e13066. https://doi.org/10.1111/apha.13066.
92. Brummelte S., Galea L.A. Chronic high corticosterone reduces neurogenesis in the dentate gyrus of adult male and female rats. *Neuroscience*. 2010;168(3):680–690. https://doi.org/10.1016/j.neuroscience.2010.04.023.
93. Laryea G., Muglia L., Arnett M., et al. Dissection of glucocorticoid receptor-mediated inhibition of the hypothalamic-pituitary-adrenal axis by gene targeting in mice. *Front Neuroendocrinol*. 2015;36:150–164. https://doi.org/10.1016/j.yfrne.2014.09.002. EDN: UWKKTD.
94. Du Preez A., Eum J., Eiben I. et al. Do different types of stress differentially alter behavioural and neurobiological outcomes associated with depression in rodent models? A systematic review. *Front Neuroendocrinol*. 2021;61:100896. https://doi.org/10.1016/j.yfrne.2020.100896. EDN: GQBJQL.
95. Kokras N., Krokida S., Varoudaki T.Z. et al. Do corticosterone levels predict female depressive-like behavior in rodents? *J Neurosci Res*. 2021;99(1):324–331. https://doi.org/10.1002/jnr.24686. EDN: KRKSJG.
96. Todkar A., Granholm L., Aljumah M. et al. HPA axis gene expression and dna methylation profiles in rats exposed to early life stress, adult voluntary ethanol drinking and single housing. *Front Molecular Neurosci*. 2016;8:90. https://doi.org/10.3389/fnmol.2015.00090.
97. Armario A., Belda X., Gagliano H. et al. Differential hypothalamic-pituitary-adrenal response to stress among rat strains: methodological considerations and relevance for neuropsychiatric research. *Curr Neuropharmacol*. 2023;21(9):1906–1923. https://doi.org/10.2174/1570159X21666221129102852. EDN: BVIBNF.
98. Atkinson L., Jamieson B., Khoury J. et al. Stress physiology in infancy and early childhood: cortisol flexibility, attunement and coordination. *J Neuroendocrinol*. 2016;28(8). https://doi.org/10.1111/jne.12408.
99. Atrooz F., Alkadhi K.A., Salim S. Understanding stress: Insights from rodent models. *Curr Res Neurobiol*. 2021;2:100013. https://doi.org/10.1016/j.crneur.2021.100013.
100. Kirby E.D., Muroy S.E., Sun W.G. et al. Acute stress enhances adult rat hippocampal neurogenesis and activation of newborn neurons via secreted astrocytic FGF2. *Elife*. 2013;2:e00362. https://doi.org/10.7554/eLife.00362.
101. Harada H., Mori M., Murata Y. et al. Dynamic changes of behavioral despair, HPA axis activity, and hippocampal neurogenesis in male rats induced by social defeat stress. *J Integr Neurosci*. 2023;22(2):43. https://doi.org/10.31083/j.jin2202043. EDN: LLFQVG.
102. Eskandari F., Salimi M., Binayi F. et al. Investigating the effects of maternal separation on hypothalamic-pituitary-adrenal axis and glucose homeostasis under chronic social defeat stress in young adult male rat offspring. *Neuroendocrinology*. 2023;113(3):361–380. https://doi.org/10.1159/000526989. EDN: IYOONP.
103. van Bodegom M., Homberg J.R., Henckens M.J.A.G. Modulation of the hypothalamic-pituitary-adrenal axis by early life stress exposure. *Front Cell Neurosci*. 2017;11:87. https://doi.org/10.3389/fncel.2017.00087. EDN: YGOSUG.
104. Suchecki D. Maternal regulation of the infant's hypothalamic-pituitary-adrenal axis stress response: Seymour 'Gig' Levine's legacy to neuroendocrinology. *J Neuroendocrinol*. 2018;30(7):e12610. https://doi.org/10.1111/jne.12610.
105. Suchecki D., Nelson D.Y., Van Oers H., Levine S. Activation and inhibition of the hypothalamic-pituitary-adrenal axis of the neonatal rat: effects of maternal deprivation. *Psychoneuroendocrinology*. 1995;20(6):169–182. https://doi.org/10.1016/0306-4530(94)00051-b.
106. Halladay L.R., Herron S.M. Lasting impact of postnatal maternal separation on the developing BNST: Lifelong socioemotional consequences. *Neuropharmacology*. 2023;225:109404. https://doi.org/10.1016/j.neuropharm.2022.109404. EDN: JOXFYQ.
107. Huang H., Wang Q., Guan X. et al. Effects of enriched environment on depression and anxiety-like behavior induced by early life stress: A comparison between different periods. *Behav Brain Res.* 2021;411:113389. https://doi.org/10.1016/j.bbr.2021.113389. EDN: NVVYER.
108. Mohammadi S., Bashghareh A., Karimi-Zandi L., Mokhtari T. Understanding role of maternal separation in depression, anxiety,and pain behaviour: a mini review of preclinical research

with focus on neuroinflammatory pathways. *Int J Dev Neurosci*. 2025;85(1):e70002. https://doi.org/10.1002/jdn.70002.
109. Pawluski J.L., Brummelte S., Barha C.K. et al. Effects of steroid hormones on neurogenesis in the hippocampus of the adult female rodent during the estrous cycle, pregnancy, lactation and aging. *Front Neuroendocrinol*. 2009;30(3):343–357. https://doi.org/10.1016/j.yfrne.2009.03.007.
110. Gobinath A.R., Workman J.L., Chow C. et al. Sex-dependent effects of maternal corticosterone and SSRI treatment on hippocampal neurogenesis across development. *Biol Sex Differ*. 2017;8:20. https://doi.org/10.1186/s13293-017-0142-x.
111. Chu S.F., Zhang Z., Zhou X. et al. Low corticosterone levels attenuate late life depression and enhance glutamatergic neurotransmission in female rats. *Acta Pharmacol Sin*. 2021; 42(6):848–860. https://doi.org/10.1038/s41401-020-00536-w. EDN: CQOIVR.
112. D'Souza Urban J.A., Shamsur R. Animal stress models in the study of stress and stress related physiological and psychological derangements. *Matrix Science Pharma*. 2018;2(1):03–05. https://doi.org/10.26480/msp.01.2018.03.05.
113. Monteiro S., Roque S., de Sá-Calçada D. et al. An efficient chronic unpredictable stress protocol to induce stress-related responses in C57BL/6 mice. *Front Psychiatry*. 2015;6:6. https://doi.org/10.3389/fpsyt.2015.00006.
114. Millstein R.A., Holmes A. Effects of repeated maternal separation on anxiety- and depression-related phenotypes in different mouse strains. *Neurosci Biobehav Rev*. 2007;31(1):3–17. https://doi.org/10.1016/j.neubiorev.2006.05.003.
115. Murthy S., Gould E. Early Life Stress in rodents: animal models of illness or resilience? *Front Behav Neurosci*. 2018;12:157. https://doi.org/10.3389/fnbeh.2018.00157.
116. Калинина Т.С., Сухарева Е.В., Дыгало Н.Н. Канонический и неканонический механизмы действия глюкокортикоидных гормонов стресса. *Успехи физиологических наук*. 2016;47(3):59–69. EDN: WMAPTV.
Kalinina T.S., Sukhareva E.V., Dygalo N.N. Canonical and non-canonical mechanisms of glucocorticoid stress hormones action. *Progress in Physiological Science*. 2016;47(3):59–69. (In Russian). EDN: WMAPTV.
117. Ramsay J.M., Feist G.W., Varga, Z.M. et al. Whole-body cortisol response of zebrafish to acute net handling stress. *Aquaculture*. 2009;297(1–4):157–162. https://doi.org/10.1016/j.aquaculture.2009.08.035.
118. Abreu M.S., Giacomini A.C.V.V., Koakoski G. et al. Divergent effect of fluoxetine on the response to physical or chemical stressors in zebrafish. *PeerJ*. 2017;5:e3330. https://doi.org/10.7717/peerj.3330.
119. Idalencio R., Kalichak F., Rosa J.G.S. et al. Waterborne risperidone decreases stress response in zebrafish. *PLoS ONE*. 2015;10(10):e0140800. https://doi.org/10.1371/journal.pone.0140800.
120. Abreu M.S., Koakoski G., Ferreira D. et al. Diazepam and fluoxetine decrease the stress response in zebrafish. *PLoS ONE*. 2014;9(7):e10322. https://doi.org/10.1371/journal.pone.0103232.
121. Barreto R.E., Miyai C.A., Sanches F.H.C. et al. Blood cues induce antipredator behavior in Nile tilapia conspecifics. *PLoS ONE*. 2013;8(1):e54642. https://doi.org/10.1371/journal.pone.0054642.
122. Barreto R.E., Barbosa A., Giassi A.C.C. et al. The 'club' cell and behavioural and physiological responses to chemical alarm cues in the Nile tilapia. *Mar Freshw Behav Physiol*. 2010;43(1):75–81. https://doi.org/10.1080/10236241003654139. EDN: NZQAXH.
123. Speedie N., Gerlai R. Alarm substance induced behavioral responses in zebrafish (Danio rerio). *Behav Brain Res*. 2008;188(1):168–177. https://doi.org/10.1016/j.bbr.2007.10.031.
124. Jameel M.K., Joshi A.R., Dawane J. et al. Effect of various physical stress models on serum cortisol level in Wistar rats. *J Clin Diagn Res*. 2014;8(3):181–183. https://doi.org/10.7860/JCDR/2014/7210.4116.
125. Jaggi A.S., Bhatia N., Kumar N. et al. A review on animal models for screening potential anti-stress agents. *Neurol Sci*. 2011;32(6):993–1005. https://doi.org/10.1007/s10072-011-0770-6. EDN: PKOKSR.
126. Jiang Y.Q., Kawashima H., Iwasaki Y. et al. Differential effects of forced swim-stress on the corticotropin-releasing hormone and vasopressin gene transcription in the parvocellular division of the paraventricular nucleus of rat hypothalamus. *Neurosci Lett*. 2004;358(3):201–204. https://doi.org/10.1016/j.neulet.2004.01.041.
127. Kothiyal P., Ratan P. Antistress effect of Fagopyrum esculentum in rats subjected to forced swimming endurance test. *Pharmacol Online*. 2011;3:290–296.
128. Cho Y.J., Kim J.H., Yim H.E. et al. Role of corticotrophin-releasing factor in the stress-induced dilation of esophageal intercellular spaces. *J Korean Med Sci*. 2011;26(2):279–283. https://doi.org/10.3346/jkms.2011.26.2.279.
129. Dayas C.V., Buller K.M., Crane J.W. et al. Stressor categorization: acute physical and psychological stressors elicit distinctive recruitment patterns in the amygdala and in medullary noradrenergic cell groups. *Eur J Neurosci*. 2001;14(7):1143–1152. https://doi.org/10.1046/j.0953-816x.2001.01733.x.
130. Godoy L.D., Rossignoli M.T., Delfino-Pereira P. et al. A comprehensive overview on stress neurobiology: basic concepts and clinical implications. *Front Behav Neurosci*. 2018;12:127. https://doi.org/10.3389/fnbeh.2018.00127. EDN: YILCKD.
131. de Kloet E.R., Joëls M., Holsboer F. Stress and the brain: from adaptation to disease. *Nat Rev Neurosci*. 2005;6(6):463–475. https://doi.org/10.1038/nrn1683. EDN: MGRRMZ.
132. Reeb B.C., Akers K.G. Is neuroplasticity of the hypothalamic-pituitary-adrenal axis maternally mediated? *J Neurosci*. 2006;26(21):5589–5590. https://doi.org/10.1523/JNEUROSCI.1275-06.2006.
133. Ulrich-Lai Y.M., Herman J.P. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci*. 2009;10(6):397–409. https://doi.org/10.1038/nrn2647.
134. Joëls M., Baram T.Z. The neuro-symphony of stress. *Nat Rev Neurosci*. 2009;10(6):459–466. https://doi.org/10.1038/nrn2632.
135. Geerling J.C., Shin J.-W., Chimenti P.C. et al. Paraventricular hypothalamic nucleus: Axonal projections to the brainstem. *J Neurophysiol*. 2010;518(9):1460–1499. https://doi.org/10.1002/cne.22283.

136. Schreck C.B., Tort L. The concept of stress in fish. *Fish Physiology*. 2016;35:1–34. https://doi.org/10.1016/B978-0-12-802728-8.00001-1.
137. Wendelaar Bonga S.E. The stress response in fish. *Physiol Rev*. 1997;77(3):591–625. https://doi.org/10.1152/physrev.1997.77.3.591.
138. Pietsch C., Konrad J., Wernicke von Siebenthal E., Pawlak P. Multiple faces of stress in the zebrafish (Danio rerio) brain. *Front Physiol*. 2024;15:1373234. https://doi.org/10.3389/fphys.2024.1373234. EDN: EPQDUF.
139. Reid S.G., Perry S.F. Storage and differential release of catecholamines in rainbow trout (Oncorhynchus mykiss) and American eel (Anguilla rostrata). *Physiological Zoology*. 1994;67(1):216–237. https://doi.org/10.1086/physzool.67.1.30163844.
140. Karege F., Perret G., Bondolfi G. et al. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry research*. 2002;109(2):143–148. https://doi.org/10.1016/s0165-1781(02)00005-7.
141. Licinio J., Wong M.L. Brain-derived neurotrophic factor (BDNF) in stress and affective disorders. *Mol Psychiatry*. 2002;7(6):519. https://doi.org/10.1038/sj.mp.4001211.
142. Radahmadi M., Alaei H., Sharifi M.R., Hosseini N. Effects of different timing of stress on corticosterone, BDNF and memory in male rats. *Physiol Behav*. 2015;139:459–467. https://doi.org/10.1016/j.physbeh.2014.12.004.
143. Chen Z.-Y., Jing D., Bath K.G. et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science*. 2006;314(5796):140–143. https://doi.org/10.1126/science.1129663.
144. Mervaala E., Fohr J., Kononen M. et al. Quantitative MRI of the hippocampus and amygdala in severe depression. *Psychol Med*. 2000;30(1):117–125. https://doi.org/10.1017/s0033291799001567. EDN: FOPFFZ.
145. Zhou C., Zhong J., Zou B. et al. Meta-analyses of comparative efficacy of antidepressant medications on peripheral BDNF concentration in patients with depression. *PloS One*. 2017;12(2):e0172270. https://doi.org/10.1371/journal.pone.0172270.
146. Gallo-Payet N., Battista M.C. Steroidogenesis — adrenal cell signal transduction. *Compr Physiol*. 2011;4(3):889–964. https://doi.org/10.1002/cphy.c130050.
147. Price J.S. An evolutionary perspective on anxiety and anxiety disorders. New insights into anxiety disorders. In Tech; 2013:3–20. https://doi.org/10.5772/52902.
148. Ghisleni G., Capiotti K.M., Da Silva R.S. et al. The role of CRH in behavioral responses to acute restraint stress in zebrafish. *Progr Neuropsychopharmacol Biol Psychiatry*. 2012;36(1):176–182. https://doi.org/10.1016/j.pnpbp.2011.08.016.
149. Liu J., Hu P., Qi X.R. et al. Acute restraint stress increases intrahypothalamic oestradiol concentrations in conjunction with increased hypothalamic oestrogen receptor β and aromatase mRNA expression in female rats. *J Neuroendocrinol*. 2011;23(5):435–443. https://doi.org/10.1111/j.1365-2826.2011.02123.x.
150. Parker M.O., Brock A.J., Walton R.T., Brennan C.H. The role of zebrafish (Danio rerio) in dissecting the genetics and neural circuits of executive function. *Front Neural Circuits*. 2013;7:63. https://doi.org/10.3389/fncir.2013.00063.
151. Andersen S.L., Lyss P.J., Dumont N.L., Teicher M.H. Enduring neurochemical effects of early maternal separation on limbic structures. *Ann N Y Acad Sci*. 1999:877(1):756–759. https://doi.org/10.1111/j.1749-6632.1999.tb09317.x.
152. Bondar N.P., Lepeshko A.A., Reshetnikov V.V. Effects of early-life stress on social and anxiety-like behaviors in adult mice: sex-specific effects. *Behav Neurol*. 2018;2018:1538931. https://doi.org/10.1155/2018/1538931. EDN: VDMICH.
153. Shams S., Khan A., Gerlai R. Early social deprivation does not affect cortisol response to acute and chronic stress in zebrafish. *Stress*. 2021;24(3):273–281. https://doi.org/10.1080/10253890.2020.1807511.
154. Ramsay J.M., Feist G.W., Varga Z.M. et al. Whole-body cortisol response of zebrafish to acute net handling stress. *Aquaculture*. 2009;297(1-4):157–162. https://doi.org/10.1016/j.aquaculture.2009.08.035.
155. Song C., Berridge K.C., Kalueff A.V. "Stressing" rodent self-grooming for neuroscience research. *Nat Rev Neurosci*. 2016;17(9):591. https://doi.org/10.1038/nrn.2016.103. EDN: WVMNFB.
156. Kalueff A.V., Stewart A.M., Song C. et al. Neurobiology of rodent self-grooming and its value for translational neuroscience. *Nat Rev Neurosci*. 2016;17(1):45–59. https://doi.org/10.1038/nrn.2015.8. EDN: WOMWGN.
157. Sperry M.M., Yu Y.-H., Welch R.L. et al. Grading facial expression is a sensitive means to detect grimace differences in orofacial pain in a rat model. *Scientific reports*. 2018;8(1):1–10. https://doi.org/10.1038/s41598-018-32297-2. EDN: KYPDNA.
158. Andresen N., Wollhaf M., Hohlbaum K. et al. Towards a fully automated surveillance of well-being status in laboratory mice using deep learning: starting with facial expression analysis. *PloS One*. 2020;15(4):e0228059. https://doi.org/10.1371/journal.pone.0228059. EDN: ASNMBX.
159. Mayo L.M., Heilig M. In the face of stress: interpreting individual differences in stress-induced facial expressions. *Neurobiol Stress*. 2019;10:100166. https://doi.org/10.1016/j.ynstr.2019.100166.
160. Brecht M., Freiwald W.A. The many facets of facial interactions in mammals. Current opinion in neurobiology. 2012;22(2):259–266. EDN: PKTKZF. https://doi.org/10.1016/j.conb.2011.12.003.
161. Song C., Liu B.-P., Zhang Y.-P. et al. Modeling consequences of prolonged strong unpredictable stress in zebrafish: complex effects on behavior and physiology. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;81:384–394. https://doi.org/10.1016/j.pnpbp.2017.08.021. EDN: XNOZPE.
162. Nicolaides N.C., Chrousos G., Kino T. et al. Glucocorticoid Receptor. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc. 2000. Available at: https://www.ncbi.nlm.nih.gov/books/NBK279171/ (accessed: 15.10.2025).
163. De Abreu M.S., Demin K.A., Giacomini A.C V.V., Amstislavskaya T.G., Strekalova T., Maslov G.O., Kositsin Y., Petersen E.V., Kalueff A.V. Understanding how stress responses and stress-related behaviors have evolved in zebrafish and mammals. *Neurobiology of Stress*. 2021;15:100405. https://doi.org/10.1016/j.ynstr.2021.100405.

Authors' info

* **Sarng S. Purveev** — Cand. Sci. (Med.), Associate Professor at the Department of Pathological Physiology with a course in Immunopathology, Saint Petersburg State Pediatric Medical University. E-mail: dr.purveev@gmail.com; https://orcid.org/0000-0002-4467-2269; SPIN: 5915-9767
Alesia S. Oskina — 5th year student, Pediatric Faculty. E-mail: alesiaoskina4@gmail.com; https://orcid.org/0009-0000-8164-2504; SPIN: 3925-1601
Sofiia V. Ulanova — 5th year student, Pediatric Faculty. E-mail: sonya.ulanovaulanova@yandex.ru; https://orcid.org/0009-0004-3809-058X; SPIN: 5825-9157

* Corresponding author.
Автор, ответственный за переписку.

Об авторах

* **Сарнг Саналович Пюрвеев** — к.м.н., доцент кафедры патологической физиологии с курсом иммунопатологии, Санкт-Петербургский государственный педиатрический медицинский университет. E-mail: dr.purveev@gmail.com; https://orcid.org/0000-0002-4467-2269; SPIN: 5915-9767
Алеся Сергеевна Оськина — студентка 5-го курса, педиатрический факультет. E-mail: alesiaoskina4@gmail.com; https://orcid.org/0009-0000-8164-2504; SPIN: 3925-1601
София Владимировна Уланова — студентка 5-го курса, педиатрический факультет. E-mail: sonya.ulanovaulanova@yandex.ru; https://orcid.org/0009-0004-3809-058X; SPIN: 5825-9157