UDC 616.346.2-002
DOI: 10.56871/RBR.2025.81.99.008

NEUROPLASTICITY OF LIMBIC STRUCTURES: CRITICAL PERIODS FOR THE FORMATION OF COGNITIVE FUNCTIONS IN ONTOGENESIS

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For citation: Pyurveev SS, Oskina AS, Ulanova SV. Neuroplasticity of limbic structures: critical periods for the formation of cognitive functions in ontogenesis. Russian Biomedical Research. 2025;10(1):70–85. DOI: https://doi.org/10.56871/RBR.2025.81.99.008

Received: 19.12.2024 **Revised: 23.01.2025** **Accepted: 09.04.2025**

Abstract. Living organisms have a unique ability to adapt to constantly changing environmental conditions. There are critical periods, also called time windows, when different areas of the brain become most sensitive to the effects of environmental factors that affect the formation of strong bonds. Mammalian neurogenesis is a lifelong process limited to certain areas of the brain, namely the subgranular zone, part of the dentate gyrus of the hippocampus, and the subventricular zone. Also, an important role in neurogenesis in primates and rodents is played by “neurogenic niches”, which are microenvironments for neuronal precursor cells and their descendants. Depending on the area of the brain, the process of neurogenesis is carried out through different mechanisms, for example, the main molecular factors of neurogenesis are the Notch and Sonic hedgehog pathways, extracellular signaling molecule and bone morphogenetic protein. The functioning of the blood-brain barrier maintains a certain chemical homeostasis and level of metabolic activity of brain tissues, which are necessary for neurogenesis. However, a number of brain structures, known as circumventricular organs, are characterized by the absence of a blood-brain barrier and a unique composition of the microenvironment, in particular the presence of chronically activated microglia in the environment, which probably affects neuro- and angiogenesis. The study of the effects of stress on the body during critical periods of neurogenesis, depending on gender, age and type of organism, duration of stress exposure, will expand the understanding of the formation of the nervous system during early ontogenesis and pathogenetic mechanisms of the development of mental disorders. In turn, the information obtained will increase the possibilities of prevention and treatment of this group of diseases.

Keywords: neuroplasticity, neurogenesis, limbic system, critical periods

DOI: 10.56871/RBR.2025.81.99.008

НЕЙРОПЛАСТИЧНОСТЬ ЛИМБИЧЕСКИХ СТРУКТУР: КРИТИЧЕСКИЕ ПЕРИОДЫ ДЛЯ ФОРМИРОВАНИЯ КОГНИТИВНЫХ ФУНКЦИЙ В ОНТОГЕНЕЗЕ

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Для цитирования: Пюрвеев С.С., Оськина А.С., Уланова С.В. Нейропластичность лимбических структур: критические периоды для формирования когнитивных функций в онтогенезе. Российские биомедицинские исследования. 2025;10(1):70–85. DOI: https://doi.org/10.56871/RBR.2025.81.99.008

Поступила: 19.12.2024 **Одобрена: 23.01.2025** **Принята к печати: 09.04.2025**

Резюме. Живые организмы обладают уникальной способностью адаптироваться к постоянно изменяющимся условиям окружающей среды. Существуют критические периоды, то есть временные окна, когда различные области мозга становятся наиболее чувствительными к воздействию окружающих факторов, влияющих на формирование прочных связей. Нейрогенез млекопитающих — процесс, протекающий на протяжении всей жизни, ограниченный определенными зонами мозга, а именно: субгранулярной зоной, частью зубчатой извилины гиппокампа и субвентрикулярной зоной. Важную роль в нейрогенезе у приматов и грызунов выполняют также «нейрогенные ниши», представляющие собой микросреды для клеток-предшественников нейронов и их потомков. В зависимости от области головного мозга процесс нейрогенеза осуществляется за счет разных механизмов. Так, основными молекулярными факторами нейрогенеза являются пути Notch и Sonic hedgehog, внеклеточная сигнальная молекула и костный морфогенетический белок. Благодаря функционированию гематоэнцефалического барьера поддерживаются определенный химический гомеостаз и уровень активности метаболизма тканей головного мозга, необходимые для нейрогенеза. Однако для ряда структур головного мозга, известных как циркумвентрикулярные органы, характерны отсутствие гематоэнцефалического барьера и уникальный состав микроокружения, в частности наличие в окружении хронически активированной микроглии, которая, вероятно, влияет на нейро- и ангиогенез. Изучение влияния стресса на организм в критические периоды нейрогенеза в зависимости от пола, возраста и вида организма, продолжительности стрессового воздействия позволит расширить представление о формировании нервной системы в период раннего онтогенеза и патогенетических механизмах развития психических расстройств. В свою очередь, полученные сведения увеличат возможности профилактики и лечения данной группы заболеваний.

Ключевые слова: нейропластичность, нейрогенез, лимбическая система, критические периоды

INTRODUCTION

Living organisms have a unique ability to adapt to constantly changing environmental conditions. There are critical periods, time windows, when different brain regions become the most sensitive to the influence of environmental factors affecting the formation of strong connections [1].

Maternal deprivation as a model of acute stress in early ontogenesis was used as an example to demonstrate its effect on biochemical parameters in cerebral structures [2]. As a result, there was a decrease in dopamine and dopamine D-1 receptor mRNA expression levels in the prefrontal cortex and amygdala, and a decrease in neuropeptide Y (NPY) levels in the basolateral amygdala and dorsal part of the hippocampus [3, 4].

Studying stress during critical periods of neurogenesis in relation to sex, age and type of the organism, as well as duration of stress exposure will allow us to expand our understanding of nervous system formation during early ontogenesis and pathogenetic mechanisms of mental disorders [5]. In turn, the obtained information will increase opportunities for prevention and treatment of this group of diseases [6].

Our review focuses on critical periods of neurogenesis, as well as on the factors that influence the development of different brain structures, including different time periods. The role of the blood-brain barrier and microglia in neurogenesis is also described. The main objective of this review is to combine and systematize data on the structures involved in neurogenesis and the factors regulating this complex process.

MECHANISMS OF REGULATION OF NEUROGENESIS IN THE POSTNATAL PERIOD

Neurogenesis is one of the key and most important and complex processes, consisting of many sequential steps, responsible for brain adaptation and repair. Local cell microenvironment, which determines further formation of neuronal networks, is considered to play a key role in the molecular mechanism controlling neurogenesis [7]. The local microenvironment triggers many processes in the so-called neurogenic niches, where successive processes of neural stem cells (NSCs) and neural progenitor cells (NPCs) transformation, migration, selection and differentiation take place.

Neurogenesis in mammals is a process that exceeds the limits of embryonic period of development. It continues throughout life but is restricted to specific brain areas such as the subgranular zone, part of the gyrus dentatus of the hippocampus and the subventricular zone located in the lateral ventricles of the brain [8].

When discussing neurogenesis and mechanisms of its regulation, it is necessary to dwell separately on the area of the infundibular recess located in the lower part of the third brain ventricle. Lining of the infundibular recess is formed by tanycytes, highly specialized bipolar cells with a long basal outgrowth [9].

Tanicites with basal outgrowths passing through the neural tissue and ending at blood vessels are represented by a specialized population of glial cells [10, 11].

Extended ends of basal outgrowths of tanycytes also end on the portal system of the pituitary gland with fenestrated capillaries, thus participating in the formation of hematoliquor and liquor-encephalic barriers [12].

Tanycytes are able to differentiate into neurons and glia and participate in the regulation of the ventromedial and arcuate nuclei. In total, four types of tanycytes are distinguished, which are different in structure, cytochemical and functional features and their location in the infundibular recess (α1-, α2-, β1- and β2-) [11, 13, 14].

Neurogenesis in adult primates and rodents is active in the olfactory bulb, where there are special areas called “neurogenic niches”. These niches are microenvironments that contain neuronal progenitor cells and their progeny. Astrocytes, oligodendrocytes, ependymal cells, capillary endothelial cells and already mature neurons surround these cells [15].

The subventricular zone (SVZ) is another brain region where neurogenesis occurs in adult animals. This zone consists of several layers (2 to 5), each containing different cell types, labeled A, B, C, and E.

Type A cells are immature neurons, neuroblasts, capable of migration. They move along the SVZ, contacting astrocytes and forming clusters near the surface of the ventricle. These cells have a specific marker, PSA-NCAM (Polysialylated-neural cell adhesion molecule), which is involved in cell adhesion, and a membrane marker, doublecortin (DCX, doublecortin).

Type B cells contain many intermediate filaments in their structure and contact the ventricular ependyma.

Type E cells (ependymal cells) are localized in the cavity of lateral ventricles, express vimentin, CD-24 (cluster definition) and S-100 protein. Due to their ability to differentiate, they are considered neuronal progenitor cells.

Type C cells are transitional cells, a transitional stage between types A and B. They have similarities with both types, making them difficult to recognize. Closely related to type A cells, however, they do not have the PSA-NCAM marker peculiar to neuroblasts, they express the transcription factor Dlx2 (Distal-Less Homeo Box 2), EGFR (epidermal growth factor receptor), Mash1 (mammalian achaete — scute homologue) [16, 17].

Three main types of cells involved in neurogenesis are distinguished in the hippocampus:

- type I cells (neuronal progenitor cells) are descendants of radial glia cells, which explains that they share common

markers such as nestin, aromatase B, Sox 1, Sox 2, BLBP (brain lipid binding protein), GLAST (glutamate/aspartate transporter), and are pluripotent (multipotent), capable of proliferation into astro- and oligodendrocytes [18];
- type II cells (intermediates) are capable of neuronal differentiation and are divided into subtypes IIa and IIb, have specific markers of neuronal differentiation — DCX, PSA-NCAM;
- type III cells (neuroblasts) become mature granular cells after migration into the gyrus dentatus; the differentiation process takes 4–7 weeks; the outgrowths of granular cells are located in the molecular layer (dendrites) and in the CA3 zone of the hippocampus (axons).

Neuroblasts migrate in chains along glial tubes, which are located along blood vessels. The endothelium of blood vessels synthesizes signaling molecules, such as BDNF (brain-derived neurotrophic factor), which stimulate migration [19].

The existence of newly differentiated cells is maintained by previously formed connections. In order to maintain a constant number of neuronal cells in the olfactory bulb, there is a mechanism for screening new cells.

The process of neurogenesis includes proliferation, differentiation, migration, and other stages regulated by multiple factors: hormones, cytokines, growth factors, and electrophysiological activity [20].

The persistence of newly formed neurons depends on the animal species and brain area. In adult Wistar line rats, neurogenesis occurs in the fascia dentata, CA1-CA4 fields of the hippocampus, cerebellar worm, and various cortical areas, but proliferation, apoptosis, and differentiation of new neurons differ in these areas. Although there is evidence of incorporation of new neurons into existing networks, their functionality is not yet fully understood [21].

FACTORS AFFECTING NEUROGENESIS IN RATS

Winstar rats demonstrated that the intensity of neurogenesis varied depending on brain areas. Certain areas, such as different parts of the cerebral cortex, cerebellar worm and CA1-CA4 fields of the hippocampus, show more active proliferation, differentiation and apoptosis of new neurons, while in other areas these processes are less pronounced [22].

At the same time, there are significant differences regarding degree and magnitude of neurogenesis between rat and human brains. Neurogenesis is essential in the gyrus dentatus of humans, as well as in the subventricular zone, where neural stem cells (progenitor cells) retain their neurogenic potential, generating a subset of interneurons of the striatum. This pathway of neurogenesis is absent in the subventricular zone in rats [23].

Rats also have a neurogenic niche formed by the NSC and its microenvironment formed by various cells: oligo- and astrocytes, capillary endothelial cells.

The process of further transformation of progenitor cells is controlled by humoral and biochemical compounds. It has been shown that administration of nitric oxide synthase inhibitor leading to inhibition of nitric oxide synthesis in the olfactory bulb, SVZ zone, and rostral migratory pathway leads to an increase in cell proliferation in these zones.

The microcirculatory system plays an important role in the paracrine regulation of neurogenesis, acting as a conductor for signaling molecules. As the brain blood vessel network ages and shrinks, the level of VEGF (vascular endothelial growth factor) decreases, which may have a negative impact on neurogenesis.

Another biochemical factor that stimulates cell proliferation and differentiation in the hippocampus is insulin growth factor (IGF-I). It is expressed in the postnatal period with a further decrease in its level during aging [24].

Thus, three main factors of age-related neurogenesis can be identified: reduction of VEGF, impaired angiogenesis, and further reduction of blood flow in cerebral vessels [22].

One of the key roles in aging process is assigned to microglia as a structure that supports apoptotic processes in the neurogenic niche as it contains factors that activate oxidase damage. Proinflammatory cytokines, in particular IL-1β and TNFα (tumor necrosis factor α), activate microglial cells, which has a negative effect on neurogenesis [22]. At the same time, microglia cells are both sources of IGF-1 and BDNF, which promote neurogenesis; their decreased activity leads to dysregulation of progenitor cell transformation in the hippocampus [25].

Hippocampus

The dentate gyrus of the hippocampus is one of the brain regions responsible for the process of neurogenesis. With the development of astrocytes followed by oligodendrocytes in the brain, neuronal activation becomes a critical factor determining synaptogenesis. Synaptic connections formed between cells can either stabilize (with sequential stimulation) or completely disappear (in the absence of stimuli).

Specifically, neurons in rodents develop from neural epithelial cells, which are considered early neural stem cells (SCs) at approximately day 9–9.5 of embryonic development and are finally formed by 15–17.5 weeks of age. The dentate gyrus of the hippocampus develops from a distinct source of progenitor cells (dentate neuroepithelium), which may have important consequences in the postnatal period [26, 27].

Hippocampal neurons develop from dentate neuro-epithelium at 13.5–17.5 weeks with the formation of the hippocampal fissure. Subsequently, the dentate progenitor cells, accumulating within the fissure, will form the future neural stem cell

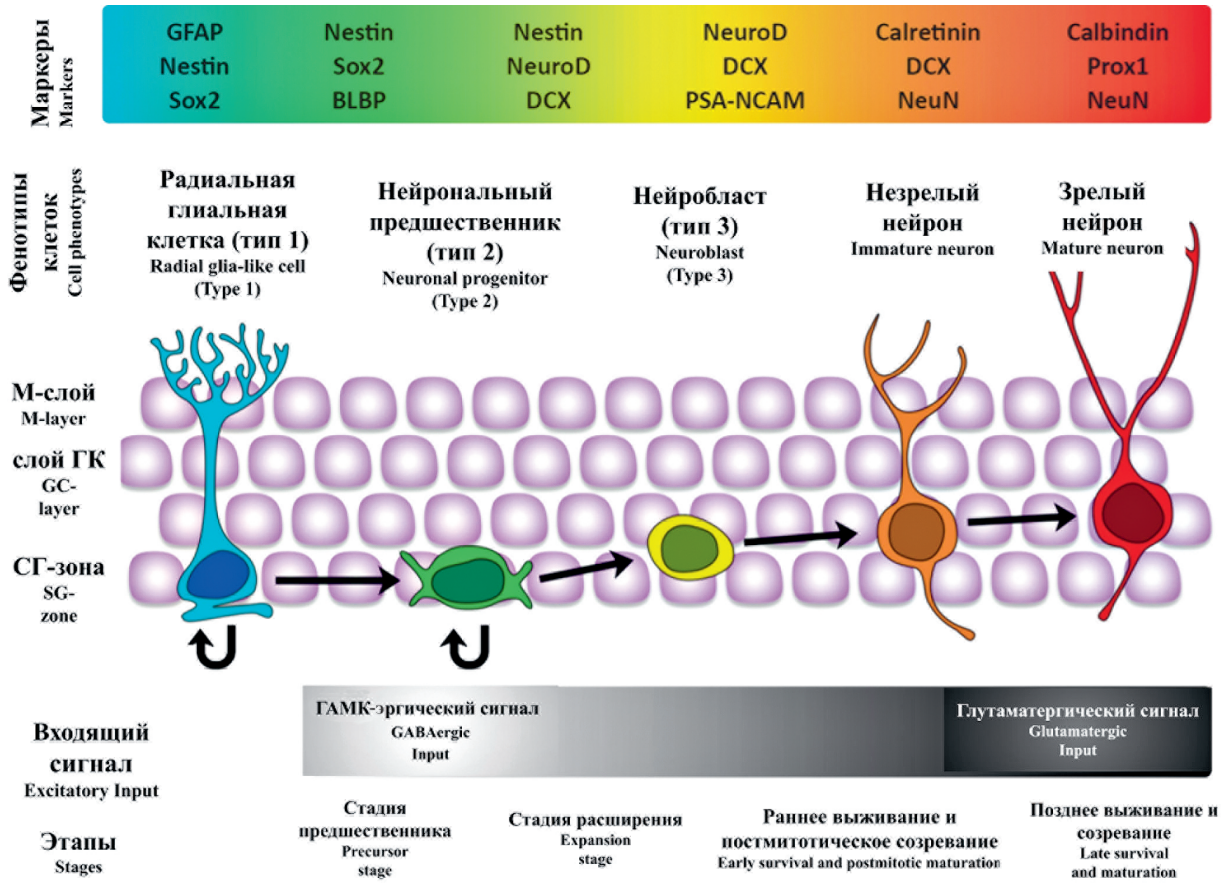


Fig. 1. Stages of hippocampal neurogenesis. Stem cells, radial glia-like (type 1; blue) maintain their pool through self-renewal and give rise to progenitor cells expressing markers with different morphologies (type 2 (A and B); green), which undergo rapid proliferation and begin to express markers necessary for subsequent cells. Type 2 cells differentiate into neuroblasts (type 3; yellow). Neuroblasts enter the early survival stage (orange cells) and extend their processes into the molecular layer. At the late stage of survival, only those neurons remain that have formed functional connections and matured morphologically (red cells). Granule neurons somata is represented in purple. The color bar at the top illustrates the gradual transition of marker expression as cells progress through different stages of neurogenesis. The gray gradient bar at the bottom indicates the switching of neurons from GABA-ergic to glutamatergic signals [26]. *Note:* M-layer — molecular layer; GC-layer — granule cell layer; SG-zone — subgranular zone; GFAP — glial fibrillary acidic protein; *Sox2* — gene *Sox2*; BLBP — brain lipid-binding protein; NeuroD — gene NeuroD (Neurogenic differentiation 1); DCX — doublecortin; PSA-NCAM — Polysialylated-neural cell adhesion molecule; NeuN — neuronal nuclei; Prox1 — Prospero homeobox protein 1

Рис. 1. Стадии гиппокампального нейрогенеза. Стволовые клетки, подобные радиальной глии (тип 1; синий), поддерживают свой пул посредством самообновления и дают начало клеткам-предшественникам, экспрессирующим маркеры различной морфологией (тип 2 (A и B); зеленый), которые подвергаются быстрой пролиферации и начинают экспрессировать маркеры, необходимые для последующих клеток. Клетки 2-го типа дифференцируются в нейробласты (тип 3; желтый). Нейробласты переходят на раннюю стадию выживания (оранжевые клетки) и распространяют свои отростки в молекулярный слой. На поздней стадии выживания остаются только те нейроны, которые сформировали функциональные связи и созрели морфологически (красные клетки). Тела гранулярных нейронов представлены фиолетовым цветом. Цветная полоса сверху иллюстрирует постепенный переход экспрессии маркеров по мере прохождения клетками различных стадий нейрогенеза. Серая градиентная полоса снизу указывает на переключение нейронов с ГАМК-эргических (ГАМК — гамма-аминомасляная кислота) на глутаматергические сигналы [26]. *Примечание:* М-слой — молекулярный слой; слой ГК — слой гранулярных клеток; СГ-зона — субгранулярная зона; GFAP — глиальный фибриллярный кислый белок (glial fibrillary acidic protein); nestin — нестин; *Sox2* — ген *Sox2*; BLBP— жиросвязывающий белок мозга (brain lipid-binding protein); *NeuroD* — ген *NeuroD* (Neurogenic differentiation 1); DCX — даблкортин (doublecortin); PSA-NCAM — молекула адгезии полисиалированных нейронных клеток (polysialylated-neural cell adhesion molecule); NeuN —нейронные ядра (neuronal nuclei); Prox1 — гомеобоксный белок 1 Просперо (Prospero homeobox protein 1); calretinin — кальретинин; calbindin — кальбиндин

layer of the adult subgranular zone or become neurons that will form the granular cell layer (Fig. 1) [28]. It is assumed that hippocampal neurogenesis can continue its development throughout life due to its increased plasticity [29, 30].

The structure of the hippocampus is heterogeneous. The dorsal hippocampus (DH) is connected to the neocortex and is mainly involved in cognitive processes, memory and learning, whereas the ventral hippocampus (VH) is connected to the amygdala and hypothalamus, playing an important role in the emotional and stress response of the organism. Inflammation in hippocampal structures can affect the functional state of neurons by modulating their synaptic plasticity. Inflammation in the structures of the central nervous system (CNS) develops faster in the DH, whereas corticosterone accumulation progresses faster in the VH and neocortex, and the DH is affected functionally (by the state of synaptic plasticity in the phenomenon of prolonged potentialization *in vivo*), and then the disorder spreads to the VH [31, 32].

There is strong evidence that neurogenesis in the adult hippocampus plays an important role in regulating memory and mood. Alterations in hippocampal neurogenesis are associated with a variety of neurological and psychiatric disorders [33, 34]. It has been shown that the period in which neurons were exposed to environmental factors (e.g., stress) will determine their further vulnerability and risk of disease [35].

Neurogenesis in the cerebral cortex

Radial glial cell (RGC) division in the cerebral cortex is regulated by the intracellular distribution of cell polarity determinants of PAR (protease-activated receptors; PAR3 and PAR6) family proteins and their regulator CDC42, which are localized at the ventricular ends of the cell pedicles.

However, these cells mainly undergo asymmetric divisions to generate a differentiated daughter cell while simultaneously renewing their pool. This process is considered as direct neurogenesis. RGCs in the forebrain undergo changes by a more complex mechanism by generating intermediate progenitor cells called basal progenitor cells (BPCs) [36]. These cells subsequently differentiate into postmitotic cells. This process is referred to as indirect neurogenesis.

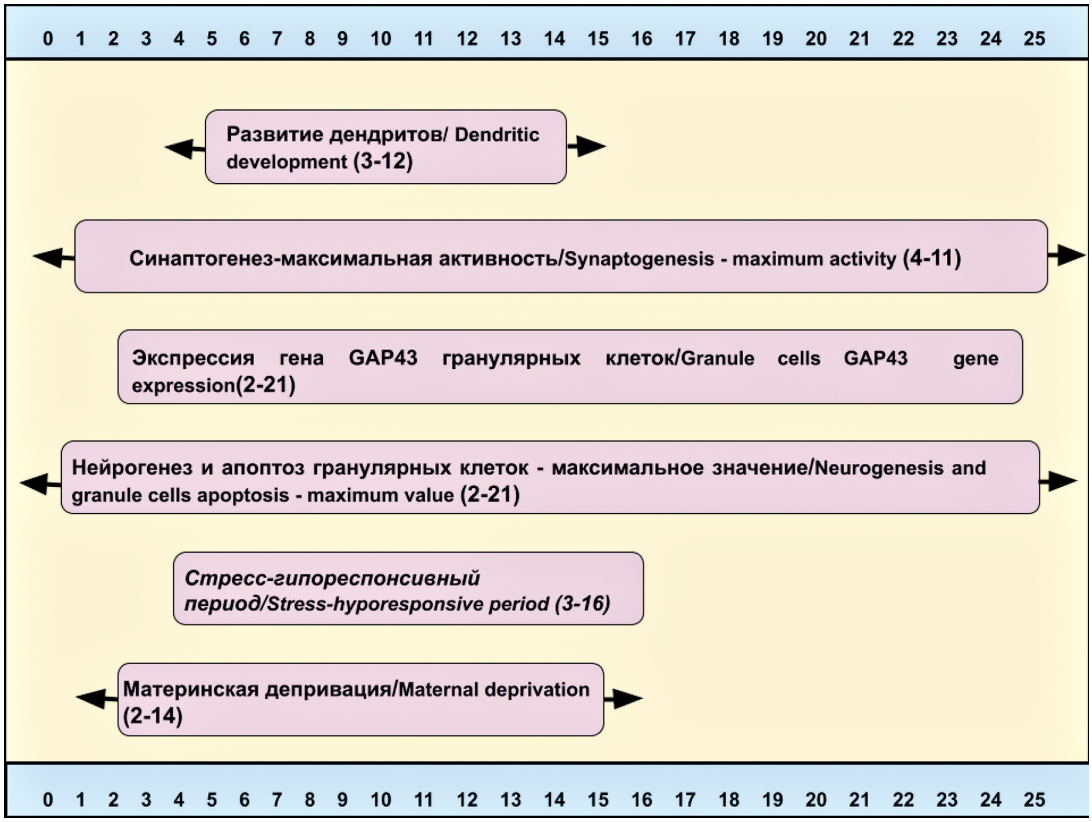


Fig. 2. **The process of neurogenesis in the postnatal period in rodents. During the newborn period, neurogenesis, myelination, apoptosis occur, as well as the processes of synaptogenesis and synaptic pruning. All these mechanisms are targets for further epigenetic modifications and the influence of environmental factors on the formation of the central nervous system [39]**

Рис. 2. **Процесс нейрогенеза в постнатальный период у грызунов. На протяжении периода новорожденности происходят нейрогенез, миелинизация, апоптоз, равно как и процессы синаптогенеза и синаптической обрезки. Все эти механизмы являются мишенями для дальнейших эпигенетических модификаций, влияния факторов окружающей среды на формирование центральной нервной системы [39]**

Neurogenesis in the brain proceeds through several stages generating different neurons. Disturbances at any stages of neurogenesis and neuronal migration can lead to impaired brain development (Figure 2). Premature transition of proliferative divisions of RGCs to the neurogenic stage can lead to their insufficient number and heterogeneity of neurons in the brain leading to microcephaly, and impaired neuronal migration can further condition lissencephaly [37, 38].

The main molecular factors of neurogenesis include:

1. Notch pathway, premature activation of which will lead to an increase in RG cell markers in the forebrain. Notch signaling promotes proliferative signaling during neurogenesis, facilitating nerve differentiation.
2. Sonic hedgehog (Shh) pathway. Shh promotes generation of oligodendrocytes and GABAergic interneurons in the ventral terminal medulla, which later infiltrate into the cortical lamina. In contrast to the ventral terminal brain, the developing cortex undergoes limited Shh signaling, the physiological role of which remains poorly understood. Reduced Shh signaling transmission in RGCs impairs their proliferation and ability to generate intermediate progenitor cells, outer RGCs, and, consequently, projection neurons. This impairment of Shh signaling causes a reduction in neuronal output, which is responsible for reducing the size of the dorsal endbrain, which may contribute to microcephaly [40].
3. Another extracellular signaling molecule, WNT, promotes the proliferative capacity of RGCs in the developing cortex. WNT has also been shown to induce neuronal differentiation of basal precursor cells, thereby providing a dual level of neurogenesis regulation.
4. In addition to WNT, bone morphogenetic protein also regulates brain cytogenesis at early stages of cortical development (12th–13th weeks of embryogenesis) and astrocytogenesis do so in later periods (14th week and afterwards) [41, 42].

Amygdala

The amygdala is part of the limbic system, responsible for expressing aggression, fear, and defensive behavior. It plays an important role in forming and retrieving emotional memories. The neural network of the amygdala is closely interconnected with other cortical areas and receives input from the thalamus, hypothalamus, and hippocampus.

The prefrontal cortex, hippocampus, amygdala, and anterior cingulate gyrus influence fear formation and are key in the development of anxiety-associated disorders. Studies show increased amygdala volume in children (age group 7–9 years) with generalized anxiety disorders, which aggravated the clinical picture [43, 44].

It has been shown that the amygdala plays the most significant role in forming emotional and social behavior in the early postnatal period. The sensitive period for the amygdala begins on postnatal day 21 and continues through childhood [45, 46].

The critical period for amygdala activity is 20–30 minutes immediately after psychotrauma, during the same period the formation of emotional memory takes place. The central region of the amygdala can inhibit GABAergic neurons, indirectly affecting the activity of the hypothalamic-pituitary-adrenal axis (HPA axis) [47, 48].

Studies by M.M. Sidor et al. showed that proinflammatory stress at an early age leads to impaired functioning of the serotonin system in young rats. It is manifested by changes in the expression of serotonin receptors and enzymes involved in its synthesis and metabolism in the neocortex, amygdala and hippocampus [49].

The amygdala, the brain region responsible for emotion processing, is also the site of corticoliberin (CL) synthesis. Corticosteroids have been found to stimulate CL production in the central nucleus of the amygdala, thus participating in regulating the effects of stress on memory [50].

Neurons of the amygdala expressing CL participate in realization of the stress response. Activation of these neurons in the central nucleus of the amygdala increases anxiety and simultaneously decreases the number of hippocampus-dependent behaviors [51]. However, a model of anhedonia induced by early stress resulted in a decrease in CL expression in the central nucleus of the amygdala by RNA interference leading to increased sucrose consumption. Thus, we can suggest a possible role for CL in the regulation of mood and motivation [5].

In summary, most anxiety disorders develop during childhood and adolescence, which is an important developmental period. They are often characterized by dynamic changes in the frontolimbic nervous system. The frontolimbic system plays a vital role in fear learning and understanding the neurobiological mechanisms associated with anxiety disorders throughout development [52, 53].

Maturation of the blood-brain barrier and its role in neurogenesis

The blood-brain barrier (BBB) is a structural and functional element of the neurovascular unit (NVU), which includes neuronal, glial, and endothelial cells. The main tasks of NVU functioning include maintaining the control of metabolism and chemical homeostasis in brain tissue, ensuring adequate blood flow in active regions, regulation of neuroplasticity processes. These tasks are reflected in a complex set of intercellular interactions in norm, stress, neurodegeneration, neuroinfection, and brain development disorders [54, 55].

The BBB development in rodents starts by E10–17, controlled permeability is formed by E21, but the development of dense contacts continues in the postnatal period as well.

Human BBB markers appear at the 8th week of embryogenesis, and intensive angiogenesis in brain tissue continues until 2–3 weeks of postnatal development [56].

It is noteworthy that the formation of barrier structures begins only after the formation of the NSC/NPC (neural stem cells/neural progenitor cells) pool and always proceeds in parallel with synaptogenesis and induction of synaptic activity in brain tissue. The formation of barrier structures also occurs in the adult brain. An integral part of this process is the formation of new microvessels with actively proliferating and differentiating endothelial progenitor cells, as well as effects of various regulatory molecules and components of cell signaling pathways (Notch, FOX (forkhead box protein), HIF-1, GSK-3 (glycogen synthase kinase 3)). In general, the association between neurogenesis and angiogenesis has been sufficiently characterized, and its disorders are recognized as a probable cause of neurogenesis suppression in the aging brain [57].

Contribution of controlled and selective permeability of the BBB in order to maintain local microenvironment in neurogenic niches is not fully understood. Currently, the effect of paracrine effector molecules produced by BBB cells on NSCs/NPCs (neural stem cells/neural progenitor cells) has been proved. Such factors include vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (FGF2, Fibroblast growth factor 2), brain-derived neurotrophic factor (BDNF), and pigment epithelium-derived factor (PEDF) [7].

The permeability of the BBB, including those in microvessels of neurogenic niches, is determined by the following factors:

1) expression of intercellular contact proteins;
2) expression of transporter and channel proteins;
3) metabolism of cerebral endotheliocytes and other NVU cells;
4) signal transduction and intercellular communication;
5) the state of the basal membrane;
6) the degree of maturity of the BBB.

In most brain regions, the BBB is formed by endotheliocytes, pericytes, and astrocytes.

Endotheliocytes are an important structure of the brain NVU and form the basis of the BBB [58]. Endothelial cells in brain microvessels are controlled by perivascular astroglia, provide selective transport of substances, sequester prothrombogenic factors and control blood rheological properties, as well as implement mechanisms of microcirculation control, and participate in the regulation of neurogenesis. They also interact with leukocytes and microglia, participating in local immune response and inflammation, and are capable of producing cytokines, metabolites, and growth factors [25, 59].

Endotheliocytes, which are part of the BBB, form barrier structures in the early period of development and participate in restoring the barrier after damage.

The features of cerebral endothelial cells are:

1) low fenestration and reduced pinocytosis;
2) high expression of intercellular contact proteins (tight junctions, adherence junctions);
3) relatively high content of mitochondria in cells;
4) close interaction with pericytes and perivascular astroglia;
5) expression of transferrin receptors, insulin receptors, and a large spectrum of transporter proteins.

All these properties provide high selectivity of the BBB, which is important for chemical homeostasis in the central nervous system. These properties help to maintain the level of glucose and other energy substrates, excretion of metabolic products, regulation of cytokine and growth factor concentrations, etc. [60, 61].

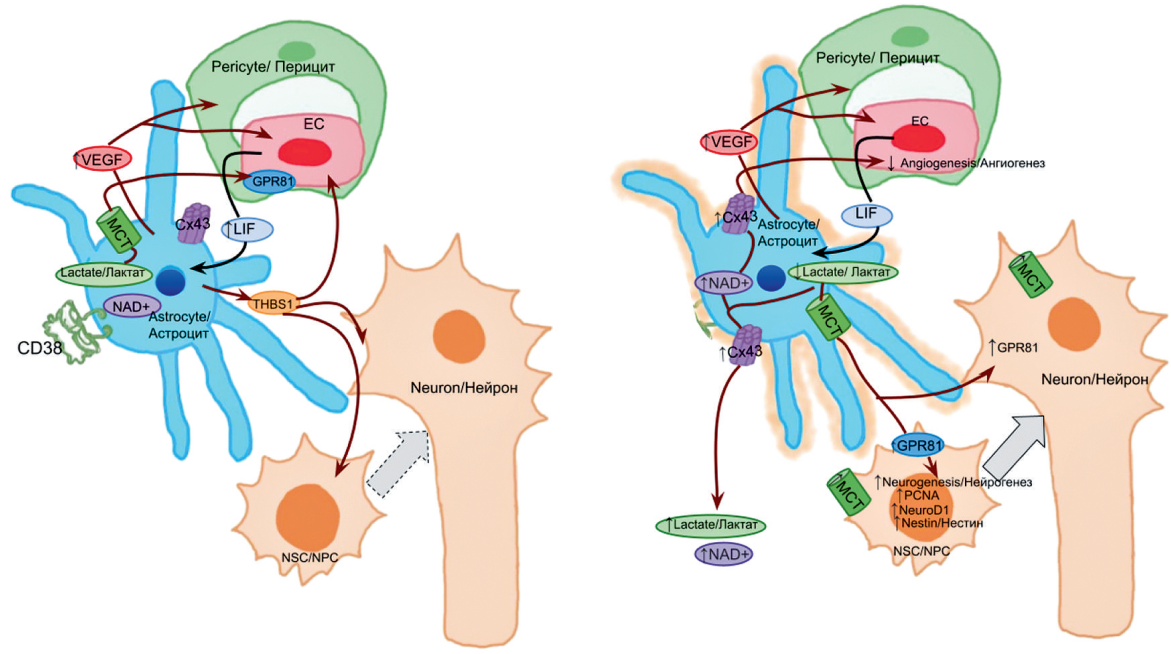
In addition to endothelial cells, neurogenesis is also controlled by perivascular astrocytes. Astrocytes also affect brain microvascular cells, for example, by causing vasodilation and stimulating angiogenesis through calcium-induced glycolysis and lactate production or generation of arachidonic acid metabolites, while astrocyte-expressed thrombospondin-1 downregulates the angiogenic potential of endothelial progenitor cells [62]. In addition, the formation of astroglial network connected via connexin channels forms a local microenvironment favorable for proliferative processes in neurogenic niches (Fig. 3).

Astrocytes in the SGZ of the hippocampus are tightly surrounded by the endothelial layer of cells, so the local microenvironment is formed mainly due to the local secretion of neuro- and gliotransmitters and growth factors, whereas in the SVZ astrocytes are loosely adjoined to the layer of endothelium and pericytes, which ensures the entry of regulatory molecules from the blood into the niche [63, 64].

Brain cell death activates the process of reparative neurogenesis in SVZ with subsequent migration of new neuroblasts to the area of damage [65].

Studies of cortical ischemia in mice have shown that this stress effect causes changes in cell proliferation in the SVZ, in which three stages can be distinguished. The first stage is an acute decrease in proliferation during the first day after cortical ischemia, then, in the second stage, the proliferation level starts to recover with reaching a maximum by day 14. The third stage is a decrease in cell proliferation by day 28 after ischemia, reaching a minimum on day 1 after ischemia. Probably, each peak in proliferation, due to increased cell division and neurogenesis, is followed by a decrease in these parameters as a result of depletion of the neurogenic niche. The decrease in cell proliferation at the first stage is probably due to increased cell migration from the SVZ to the olfactory bulb region [66].

These same events are accompanied by activation of cerebral angiogenesis, probably as a compensatory mechanism in



а / a *б / b*

Fig. 3. Scheme of neuron-glial coupling and interaction of astrocytes with other cells of the blood-brain barrier under normal conditions (*a*) and during activation of astrocytes (*b*). Brown arrows show the influence of astrocytes on other types of cells, the black arrow shows the influence of endothelial cells on astrocytes [7]. *Note:* EC — endothelial cells; MCT — monocarboxylate transporter; VEGF — vascular endothelial growth factor; LIF — leukemia inhibitory factor; Cx43 — connexin 43; CD38 —claster definition 38; GPR81 — hydroxycarboxylic acid receptor 1 (HCA1), G protein-coupled receptor 81; THBS1 — thrombospondin 1; NSC/NPC — Neural stem / neural progenitor cell; PCNA — proliferating cell nuclear antigen; NeuroD1 — neurogenic differentiation 1; NAD+ — nicotinamide adenine dinucleotide

Рис. 3. Схема нейрон-глиального сопряжения и взаимодействия астроцитов с другими клетками гематоэнцефалического барьера в обычных условиях (*а*) и при активации астроцитов (*б*). Коричневые стрелки отображают влияние астроцитов на другие виды клеток, черная стрелка показывает влияние эндотелиоцитов на астроциты [7]. *Примечание:* EC — эндотелиальные клетки (endothelial cells); MCT — монокарбоксилатный транспортер (monocarboxylate transporter); VEGF — сосудисто-эндотелиальный фактор роста (vascular endothelial growth factor); LIF — лейкемия-ингибирующий фактор (leukemia inhibitory factor); Cx43 — коннексин 43; CD38 — кластер дифференцировки 38 (claster definition 38); GPR81 — рецептор лактата 81, рецептор, связанный с G-белком 81 (hydroxycarboxylic acid receptor 1 (HCA1), G protein-coupled receptor 81); THBS1 — тромбоспондин 1 (thrombospondin 1); NSC/NPC — нормальные промежуточные клетки/нормальные стволовые клетки (neural stem/neural progenitor cell); PCNA — маркер пролиферирующих клеток (proliferating cell nuclear antigen); NeuroD1 — фактор нейрогенной дифференцировки-1 (neurogenic differentiation 1); NAD+ — никотинамидадениндинуклеотид (nicotinamide adenine dinucleotide)

response to tissue damage and reduced perfusion, for example, after ischemic brain injury or in slowly progressive degenerative diseases of the nervous system. The permeability of new vessels is increased in these situations and this is probably related to both neuroinflammation and the need to create new areas of neurogenesis in the damaged brain. The Notch signaling pathway conversion is one of the mechanisms, whereby endothelium and pericytes of cerebral microvessels are able to express the Notch receptor ligand Delta-like ligand-4 (DLL4) in response to high local production of VEGF [67]. This mechanism stimulates Notch proliferation and initiates the formation of additional neurogenic niches in the brain ventricular walls.

It is interesting to note that a number of brain structures are characterized by the absence of the BBB. These areas, known as circumventricular organs, contain highly permeable fenestrated capillaries. Circumventricular organs include the medial eminence, subfornical organ, vascular plexus, etc. For some circumventricular organs, the presence of neural stem cell niches has been suggested [15]. From this point of view, it seems important to note some features of the microenvironment characteristic of circumventricular organs that may influence the process of neurogenesis. One of such features is the presence of chronically activated microglia in circumventricular organs. Thus, it has been demonstrated that microglia of the medial eminence are characterized by morphological signs of activation throughout postnatal ontogenesis, despite the absence of pathology [17].

The presence of highly activated microglia in circumventricular organs in the mouse has been demonstrated under physiologi-

cal conditions [68]. It is important to note that microglia express high levels of CD16/32, CD86 — markers of M1 phenotype of macrophages responsible for proinflammatory response, endotoxicity and activation of phagocytosis, as well as CD206 — markers of M2 phenotype of macrophages regulating the phases of resolution of inflammation and repair of damaged tissues.

Reasons for this state of microglia are not fully understood, but studies performed on adult mice emphasize the importance of these markers for neurogenesis: microglia activated by endotoxins block neuro- and oligodendrocytogenesis, while microglia activated by such cytokines as interleukin-4 and interferon-γ stimulate neurogenesis, further emphasizing the influence of microglial phenotype on NSC/NPC renewal [68].

In this case, microglia activation is represented by the fact that the total length and number of outgrowths of microglial cells are significantly shorter than in other brain regions, and on the contrary, the expression level of activation marker molecules is elevated. Presumably, this is due to specific features of the structural and functional organization of these organs. In particular, this is due to the constant contact of microglia in circumventricular organs with molecules circulating in blood [36]. A probable function of microglia may be phagocytosis of neurotoxic molecules coming from the bloodstream in order to maintain a normal microenvironment in circumventricular organs.

Another possible function of activated microglia is regulating blood vessel permeability and angiogenesis [68, 69]. Intensive angiogenesis accompanied by constant proliferation and apoptosis of endothelial cells in blood vessels is carried out in circumventricular organs. In turn, the ability to regulate the proliferative activity of endothelium, as well as to participate in the removal of apoptotic cells remaining from dead endothelial cells has been indicated for activated microglia [58].

Finally, microglia can be involved in neurogenesis and acquire an activated morphotype [70–73]. Thus, it allows us to suggest a possible contribution of activated microglia to form neurogenic niches in this organ. This was previously observed in subventricular zone of the lateral ventricles and subgranular zone of the dentate gyrus of the hippocampus [74].

CONCLUSION

Mechanisms of neurogenesis in the postnatal period, as well as the processes of neuronal differentiation and migration are extremely important. The features of neurogenesis processes in different brain regions, using the hippocampus, cerebral cortex, and amygdala as examples, are interesting during critical periods of neurogenesis, the so-called time windows, both in intrauterine and postnatal periods. There is no doubt that the blood-brain barrier and microglia cells play a special role in forming microenvironment as well as influence neurogenesis in future.

Studying stress effect during critical periods of neurogenesis is promising both in theoretical and applied direction in order to develop methods of prevention and therapy of mental diseases, including neurodegenerative diseases.

ADDITIONAL INFORMATION

Author contribution. Thereby, 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.

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

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.

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

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