

MOLECULAR AND CELLULAR ASPECTS OF NEUROIMMUNE REGULATION OF THE CENTRAL NERVOUS SYSTEM

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ABSTRACT

In recent years, neuroimmune regulation of central nervous system functions has been considered as a fundamental mechanism for maintaining homeostasis, ensuring the integration of nervous, immune and endocrine processes. The accumulated data suggest that immune signals are not exclusively a manifestation of inflammation, but represent a physiological component of the regulation of synaptic plasticity, neurogenesis, and adaptive responses of the brain. In this case, microglia, astrocytes, the endothelium of the blood-brain barrier, and molecular mediators, including cytokines, chemokines, and intracellular signaling cascades, play a key role. This review systematizes modern concepts of cellular and molecular mechanisms of neuroimmune interaction, analyzes their involvement in maintaining neural network homeostasis and cognitive processes, as well as the effects of stress and systemic inflammation on the regulatory circuits of the central nervous system. Special attention is paid to the problem of the boundaries of the physiological norm and the mechanisms of transition from adaptive neuroimmune activation to chronic neuroinflammation. The integrative aspects of neuroimmune regulation in the context of systemic adaptation and prospects for further research are considered. Generalization of data on regulatory nodes and mechanisms of reversibility of immune activation can contribute to the development of pathogenetically based and personalized approaches to the prevention and correction of neurodegenerative and stress-induced disorders.

KEYWORDS: neuroimmune regulation, microglia, astrocytes, cytokines, neuroinflammation, synaptic plasticity, stress, CNS homeostasis.

INTRODUCTION

Neuroimmune regulation of the functions of the central nervous system is considered today as one of the key directions of modern physiology, since it combines the concepts of nervous, immune and endocrine integration in maintaining homeostasis [1]. For a long time, the central nervous system has been interpreted as an "immune-privileged" structure, relatively isolated from peripheral immune influences by barrier mechanisms, but the accumulated data have significantly changed this view. It became obvious that immune processes are not opposed to brain physiology, but are embedded in it as a regulatory component that ensures adaptation, plasticity, and stability of neural networks [2-3].

At the center of these concepts is microglia, a specialized population of resident immune cells in the brain that normally performs fine monitoring of neural activity and the state of the intercellular environment. Microglial cells are involved in synaptic remodeling, regulation of neurogenesis, and utilization of cellular elements, thereby forming the morphofunctional foundations of adaptation. In recent years, it has been shown that microglia are able to quickly change

their functional state in response to fluctuations in neural activity, affecting signal transmission parameters and maintaining the boundaries of the physiological norm [4].

An equally important role is played by astrocytes, which have been reinterpreted from passive "supporting" elements as active participants in neuroimmune interaction. Astrocytes ensure the structural and functional integrity of the bloodbrain barrier, regulate the metabolic supply of neurons, and participate in immune signaling through the synthesis of cytokines and chemokines. Their heterogeneity and plasticity indicate a high degree of regional specialization and involvement in local neural network processes [7-10].

The discovery of the meningeal lymphatic pathways has further expanded the understanding of neuroimmune regulation, showing that the exchange of immune signals between the central nervous system and the periphery has a structural basis. These data called into question the previous model of complete brain isolation and raised the question of the mechanisms of immune surveillance in physiological conditions [8].

Despite a significant amount of research, the problem of the boundaries of physiological neuroimmune activity remains open. To date, it has not been clearly defined where the transition from adaptive immune regulation to maladaptive neuroinflammation takes place [9]. It is known that short-term activation of glial cells can perform a protective function, contributing to tissue repair and maintaining plasticity, while chronic activation disrupts synaptic organization and neurogenesis. However, the mechanisms of this transformation, as well as the criteria for its early recognition, require further analysis [12].

The problem becomes particularly relevant in the context of traumatic and neurodegenerative processes, in which secondary immune responses have a significant impact on the outcome. In conditions of traumatic brain injury or chronic neurodegeneration, it is the neuroimmune mechanisms that largely determine the dynamics of damage recovery or progression [14]. At the same time, it remains debatable which changes are compensatory and which are beyond the limits of the physiological norm. Thus, neuroimmune regulation should be considered not only as a defense mechanism, but also as a component of the overall adaptive system of the brain. Understanding the intercellular communication between neurons, microglia, and astrocytes, as well as the role of cytokine and neurotransmitter signaling, is of fundamental importance for modern physiology.

The purpose of the review is to analyze modern concepts of cellular and molecular mechanisms of neuroimmune regulation of CNS functions, with an emphasis on adaptive processes and the limits of their physiological stability.

The historical development of ideas about neuroimmune interactions in physiology

The formation of ideas about neuroimmune interactions in physiology has gone a long way - from single observations of the brain's response to inflammation to the concept of continuous dialogue between the nervous and immune systems [16]. In the early stages of the development of physiology, the central nervous system was considered as an isolated structure, and immune processes as peripheral and autonomous. However, already in the middle of the 20th century, data appeared indicating the influence of brain structures on immune responses, which became the starting point for the emergence of neuroimmunophysiology. One of the fundamental shifts was the recognition that the immune system performs not only an effector, but also a sensory function, recognizing genetically foreign agents and forming signals capable of influencing central regulatory mechanisms [20]. This concept significantly expanded the scope of physiology, as the immune system began to be considered as a source of specific information for the brain. Electrophysiological studies have shown that the introduction of antigens is accompanied by rapid changes in the activity of hypothalamic and limbic structures, which indicated the existence of pathways for transmitting immune information to the central nervous system [18].

An important stage was the identification of humoral mediators, primarily cytokines, capable of acting as signal carriers from immune cells to nerve centers. The discovery of the role of interleukin-1 in the activation of the hypothalamic-pituitary-adrenal axis demonstrated that immune signals can trigger endocrine reactions affecting systemic homeostasis. This allowed us to talk about the formation of the neuro-immune-endocrine regulatory axis as a single functional system [19]. It was essential to establish the synthesis of hormones and neuropeptides by cells of the immune system, which destroyed the idea of a strict separation of mediator systems. The detection of common receptors for cytokines, hormones, and neurotransmitters on the cells of both systems confirmed the presence of a universal chemical language of intersystem interaction [22]. Historically, the concept of two-way signal exchange has developed, in which each system is able to initiate a response from the other. For a long time, the humoral path of information transmission was considered the main one, but the development of morphological and neurovirological methods made it possible to identify the anatomical foundations of the nervous afferentation of immune organs [25]. Studies of the innervation of the spleen, thymus, and bone marrow have shown the presence of sympathetic connections with central structures, and studies on the role of the vagus nerve have demonstrated the involvement of parasympathetic pathways in signaling inflammation. These data have significantly expanded the understanding of the speed and specificity of neuroimmune dialogue [30].

In parallel, the concept of the "inflammatory reflex" was formed, in which the activation of afferent fibers of the vagus during immune stimulation triggers efferent anti-inflammatory mechanisms. Historically, this has become an important proof that the nervous system not only receives information about immune events, but also actively regulates their intensity [18-20]. Later, it was shown that the pattern of activation of brain structures depends on the nature of the antigen, which indicates the possibility of encoding specific immune information in neural networks [32]. A special place in the historical development is occupied by the opening of the "gates" of immune cell penetration into the central nervous system in autoimmune models, which allowed for a new look at the mechanisms of multiple sclerosis and other

neuroimmune diseases. These data demonstrated that neuroimmune interaction includes not only signaling, but also cellular mechanisms [34].

In recent decades, the field of neuroimmunology has expanded significantly, going beyond the classical inflammatory diseases of the nervous system. The range of studies included neurodegenerative processes, aging, the effects of microbiota, neurogenesis, and even behavioral disorders. This reflects the evolution of the approach from the study of pathological conditions to the analysis of the role of the immune system in the normal development and functioning of the brain [37]. At the same time, the historical development of ideas about neuroimmune interactions in physiology is characterized by a transition from the idea of isolation to an understanding of the integration of systems. The current stage is determined by the search for mechanisms to maintain a balance between adaptive immune regulation and pathological inflammation [40]. Despite the considerable amount of accumulated data, questions remain about the priority of sympathetic and parasympathetic pathways, the mechanisms of encoding immune information, and the limits of the physiological norm of neuroimmune reactions. Further research in this area is of fundamental importance for the development of fundamental physiology and the development of new regulatory therapeutic approaches.

Cellular components of neuroimmune regulation: neurons, microglia, astrocytes, endothelium of the blood-brain barrier

If we consider neuroimmune regulation in the logic of modern physiology, it is necessary to proceed from the idea of the brain as an integral functional system in which neurons, microglia, astrocytes, and the endothelium of the blood-brain barrier act as interconnected elements of a single regulatory circuit [15]. A neuron, being a specialized cell providing the generation and conduction of electrical signals, realizes its function only under conditions of constant structural, metabolic and immune support from the glia and vascular component. It is significant that a clinical and physiological study by E.V. Boklazhenko, G.M. Bodienkova, and O.I. Shevchenko (2023) demonstrated a reliable relationship between changes in immunological parameters and the level of constant brain potential in patients with vibration disease, which indicates a direct correlation between immune activation and the bioelectric state of neural networks. Thus, it was confirmed that immune shifts are reflected at the level of integrative neurophysiological regulation and are realized through cellular mechanisms of neuroimmune interaction.

In this context, it becomes obvious that neuronal activity cannot be interpreted in isolation from the functions of nonneuronal cells. Astrocytes support ionic and mediator homeostasis, provide neurons with energy substrates, and participate in the regulation of local blood flow by linking synaptic activity with vascular response [42]. Microglia carry out constant immune surveillance, monitor the state of synaptic contacts and, if necessary, initiate their elimination or remodeling. Oligodendrocytes form myelin sheaths, providing trophic support and optimizing pulse conduction. In case of damage or functional stress of neurons, it is microglia and astrocytes that first activate response programs, including morphological restructuring, proliferation, cytokine synthesis, and phagocytic activity, which reflects the tissue response of the central nervous system to stress or degenerative processes [44].

From the standpoint of evolutionary physiology, the regulatory mechanisms of the brain were formed in conditions focused on ensuring survival and reproductive success, however, an increase in human life expectancy led to the appearance of conditions to which these mechanisms are not fully adapted [45]. In this aspect, neuroinflammation should be considered as a universal response capable of performing both protective and damaging functions. In the fundamental review by Adamu A. and co-authors. (2024) Neuroinflammation is presented as a central link in the pathogenesis of neurodegenerative diseases, where microglia act as a key mediator of pro-inflammatory signals affecting neuron survival, synaptic plasticity, and cellular bioenergetics. The authors emphasize the importance of cytokine cascades, mitochondrial dysfunction, and energy metabolism disorders as factors that translate an adaptive response into a chronic pathological process.

Developing a systematic understanding of these mechanisms, Müller L., Di Benedetto S. and Müller V. (2025) showed that the transition from homeostasis to neuroinflammation is due not to isolated activation of individual cells, but to a profound restructuring of intercellular interactions within the neurovascular unit. Their work substantiates the concept of network dynamics, according to which astrocytes coordinate signals between neurons and the endothelium of the bloodbrain barrier, and microglia change their functional profile depending on a set of local molecular stimuli [46]. Thus, it is emphasized that the inflammatory response in the central nervous system is the result of a cooperative restructuring of the cellular ensemble, rather than a linear chain of events.

Of particular importance for understanding this system is the ontogenetic origin of microglia, which colonize the brain in the early stages of development before the formation of the blood-brain barrier and form a self-sustaining population with a unique transcriptomic profile [47]. In the early postnatal period, microglia demonstrate maximum phenotypic variability and participate in the formation of neural networks through complement-dependent synaptic pruning and the CX3CL1–CX3CR1 signaling axes. In the adult brain, it retains surveillance functions, responding to changes in membrane potential, ATP release, and damage signals, while epigenetic mechanisms subtly regulate its phagocytic and secretory activity [48]. It is precisely this constant regulation and sensitivity of microglia to changes in the internal environment of the brain that make it possible to consider its work not separately, but as part of the overall coordinated activity of all cellular components of the central nervous system.

Molecular mechanisms of neuroimmune signaling: cytokines, chemokines, receptor and intracellular cascades The molecular mechanisms of neuroimmune signaling form the basis for the integration of immune and neuronal processes in

the central nervous system. Cytokines and chemokines are of key importance in their structure, providing intercellular communication between neurons, microglia, astrocytes, and the endothelium of the blood-brain barrier [50]. These mediators act through specific receptor complexes that trigger intracellular signaling cascades. Binding of cytokines to membrane receptors leads to activation of tyrosine kinase systems and phosphorylation of signaling proteins. One of the central pathways is the JAK/STAT cascade, which regulates the transcription of inflammatory and adaptive response genes. In parallel, MAPK and PI3K/Akt-dependent mechanisms that determine cell survival and metabolic restructuring are activated [19].

The transcription factor NF- κ B, which controls the expression of pro-inflammatory genes, plays an important role in the implementation of neuroimmune signaling. Its activation occurs in response to stimulation of IL-1 β , TNF- α , and Tolllike receptors of innate immunity [27]. Under physiological conditions, this mechanism provides adaptive regulation, whereas with prolonged activation it contributes to the chronization of inflammation. Chemokines, interacting with Gprotein-coupled receptors, form the spatial organization of the cellular response. Signaling axes such as CX3CL1–CX3CR1 and CXCL12–CXCR4 regulate cell migration and the direction of microglial processes [52].

The activation of chemokine receptors is accompanied by the mobilization of intracellular calcium and the activation of secondary mediators, including phospholipase C and protein kinases. These processes integrate with mitochondrial and metabolic mechanisms, forming a single functional cell response [53]. The metabolic restructuring of microglia and astrocytes upon activation determines the spectrum of secreted cytokines and the intensity of the inflammatory response. Epigenetic mechanisms regulating the sensitivity of cells to signaling stimuli are essential. Chromatin modifications and histone deacetylase activity form a transcriptional profile that determines the nature of the immune response [53]. Table 1 systematizes the main cytokines, chemokines, corresponding receptors and involved intracellular cascades, which makes it possible to visualize their functional relationship.

Table 1: The main molecular components of neuroimmune signaling in the central nervous system

Mediator / system	Cellular sources in the central nervous system	The main receptors	Key intracellular cascades and effects
IL-1 β	Microglia, astrocytes	IL-1R1	NF- κ B, MAPK; induction of proinflammatory genes, modulation of synaptic plasticity
TNF- α	Microglia, astrocytes	TNFR1, TNFR2	NF- κ B, JNK, PI3K/Akt; regulation of neuronal survival, excitotoxicity in excess
IL-6	Microglia, astrocytes, neurons	IL-6R/gp130	JAK/STAT3; modulation of inflammatory response and neurogenesis
TGF- β	Astrocytes, microglia	TGF- β R I/II	SMAD-dependent pathways; antiinflammatory regulation, maintenance of homeostasis
IL-10	Microglia	IL-10R	JAK/STAT3; limitation of inflammatory activation
CX3CL1 (fractalkine)	Neurons	CX3CR1 (microglia)	PI3K/Akt, MAPK; control of microglial activation and synaptic elimination
CXCL12	Astrocytes, BBB endothelium	CXCR4	G-protein-dependent cascades, MAPK; cell migration, regulation of neuroplasticity
ATP (purinergic signaling)	Neurons, astrocytes	P2Y12, P2X7	Ca ²⁺ -dependent pathways, NF- κ B; activation of microglia, phagocytosis
Toll-like receptors (TLR4)	Microglia, astrocytes	TLR4	MyD88-dependent pathway, NF- κ B; innate immune response
Complement (C1q, C3)	Microglia, astrocytes	CR3	Phagocytic mechanisms; synaptic elimination

Note. BBB – blood-brain barrier; NF- κ B – nuclear factor κ B; MAPK– mitogen-activated protein kinases; JAK/STAT – Janus-kinases/Signal Transducer and Activator of Transcription; PI3K/Akt – phosphoinositide-3-kinase/protein kinase B; SMAD – signaling proteins TGF- β ; TLR – Toll-similar receptors.

The presented data demonstrate that the molecular mechanisms of neuroimmune signaling represent a multilevel regulatory system. The balance between the activation and limitation of these cascades determines the boundaries of the physiological norm and the resistance of the central nervous system to damaging effects. Consequently, these signaling cascades are implemented at the level of specific cell populations of the central nervous system. In this regard, the physiological role of microglia and astrocytes in maintaining neural network homeostasis is of particular importance.

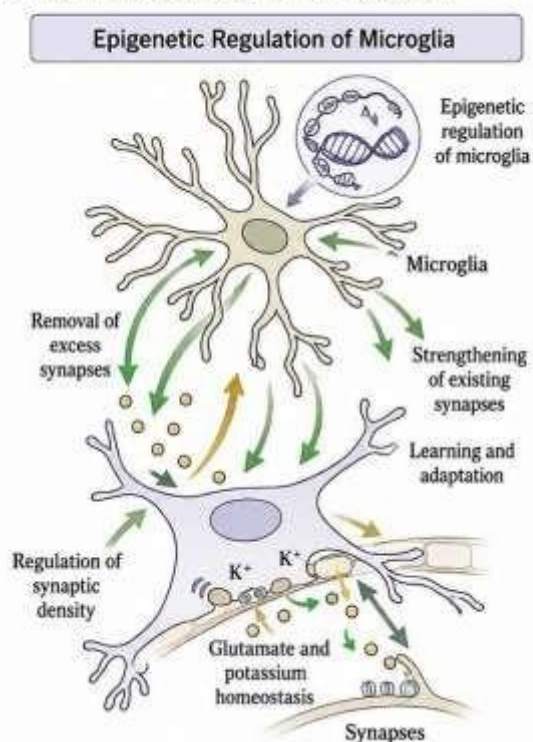
The physiological role of microglia and astrocytes in maintaining neural network homeostasis

In modern neuroscience, special attention is paid to the physiological role of microglia and astrocytes in maintaining neural network homeostasis, since it is these glial cells that create and regulate the internal environment that ensures the stable functioning of neural networks [54]. Recent studies have shown that microglia are normally not a passive "immune observer", but are actively involved in controlling synaptic density, removing excess contacts, and maintaining an optimal level of neural activity [55]. New molecular methods and genetic models have made it possible to clarify that in a healthy brain, microglia regulate the formation of neural circuits, participate in learning and adaptation mechanisms, thereby maintaining the stability of the neural network architecture.

Epigenetic regulation of microglial functions is of particular importance, since, as shown by Scholz R, Brösamle D, Yuan X, Beyer M, Neher JJ (2024), it is epigenetic mechanisms that determine the nature of its immune and homeostatic responses in the central nervous system. Understanding these physiological processes is important not only for interpreting pathology, but also for understanding how the balance between arousal and inhibition in neural networks is normally maintained. In the context of neural network homeostasis, astrocytes perform an equally important function, providing metabolic support for neurons, regulating the concentration of ions and neurotransmitters in the synaptic space. Under physiological conditions, they control the level of glutamate and potassium, preventing excessive arousal and thereby stabilizing the work of neural ensembles. When exposed to damaging factors, astrocytes can enter various activated states, but even these changes are initially aimed at preserving the structural and functional integrity of the network [47]. The "A1" and "A2" phenotypes isolated in neuroinflammation reflect the spectrum of astroglia reactions, but this classification is conditional and does not exhaust the full variety of their functional states. Transcriptomic studies show that some reactive astrocytes are able to enhance synaptic remodeling processes, while other subpopulations contribute to the survival of neurons and the restoration of intercellular connections [35]. The control of these functional states is largely determined by the activation of signaling cascades that converge on inflammatory transcription factors, forming key molecular nodes that ensure astrocyte switching between different activity programs. The central place among these mechanisms is occupied by NF κ B, whose nuclear translocation determines the severity of the inflammatory response and, consequently, the degree of influence of astrocytes on neural activity [39].

However, under normal conditions, the activity of NF κ B is strictly limited, which prevents excessive cytokine production and maintains the stability of neural networks. Pro-inflammatory cytokines and innate immunity receptors are among the factors capable of triggering this pathway, but their action is normally balanced by endogenous suppression mechanisms [55]. Thus, signaling cascades associated with sphingosine-1-phosphate receptors and lipid mediators can enhance the astroglial response, thereby affecting the interaction of astrocytes and microglia. At the same time, there are mechanisms that limit excessive activation, including the effect of tryptophan metabolites and signals from the gut-brain axis, which emphasizes the systemic nature of regulation of neural network homeostasis [57]. Astrocytes also interact with microglia through cytokines and growth factors, forming closed regulatory circuits, shown in Figure 1, which shows the two-way effect of these cells on each other. Microglia, in turn, are able to induce changes in the astrocyte phenotype through the release of IL-1 α , TNF- α and complement components, which affects the state of synapses and the level of neurotrophic support.

A Maintenance of Neural Homeostasis



B Interaction of Microglia and Astrocytes

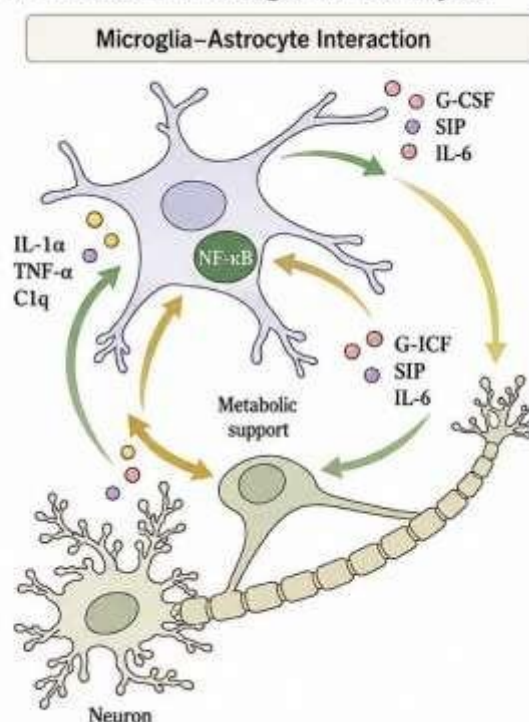


Figure 1: The physiological role of microglia and astrocytes in maintaining neural network homeostasis and their molecular mechanisms of interaction

The mechanisms shown in the figure reflect the complexity and interconnectedness of the signaling pathways through which microglia and astrocytes coordinate their functions under normal conditions. These data emphasize that their interaction goes beyond the inflammatory response and is an integral part of maintaining neural network homeostasis. Thus, the considered molecular and cellular processes allow a new assessment of the contribution of glial cells to the regulation of neural network activity. It should be noted that the physiological role of microglia and astrocytes is not only in immune protection, but also in the constant tuning of neural circuits, where their coordinated activity ensures stability, adaptation and functional integrity of the central nervous system.

Neuroimmune mechanisms of synaptic plasticity and cognitive processes

Synaptic plasticity and cognitive processes are formed with the active participation of immune signals integrated into the central nervous system and providing dynamic regulation of the internal balance of the body. The connection between these systems goes beyond defensive reactions and represents a constant exchange of signals necessary for the normal development and functioning of the central nervous system [58]. Immune cells and their molecular mediators are involved in the formation of neural circuits, determining the density and stability of synaptic contacts [60].

In the parenchyma of the brain, microglia continuously monitor the state of synapses, participate in their selective elimination during development, and continue to regulate their structure in the adult brain. Due to these processes, microglia affect the accuracy of neural connections, providing optimal conditions for learning and memory formation. Cytokines, including IL-1b and TNF, are released in response to neuronal activity and are able to alter the efficiency of synaptic transmission [54]. In physiological concentrations, they are involved in the regulation of long-term potentiation and depression, affecting the processes of memory consolidation. Maintaining a balanced activity of the immune system is a prerequisite for maintaining normal cognitive function [61]. Disorders of immune regulation are accompanied by changes in neurogenesis, decreased plasticity, and the formation of cognitive deficits. These facts indicate that neuroimmune signals are an important component of learning and adaptation mechanisms [63].

Astrocytes and oligodendrocytes play an important role in neuroimmune regulation, affecting synaptic integration and the rate of conduction of impulses. Oligodendroglia are able to respond to immune stimuli, participating in maintaining the integrity of myelin and, consequently, in ensuring cognitive efficiency. Through cytokine receptors, oligodendrocytes are involved in the processes of intercellular communication, which affects the functional organization of neural networks [60]. Astrocytes interact with oligodendrocytes and regulate remyelination, contributing to the restoration of signal transmission after injury. In addition, oligodendrocytes can secrete mediators that activate signaling pathways in astrocytes and alter the nature of the neuroimmune response. The interaction of astrocytes and neurons is of central importance for maintaining synaptic balance, since astrocytes control the concentration of glutamate and potassium ions in the synaptic space [47].

Activation of inflammatory signaling cascades in astrocytes can lead to excessive production of nitric oxide and impaired synaptic stability. The metabolic support of neurons through the lactate shuttle mechanism is also part of the neuroimmune regulation of plasticity. A decrease in the effectiveness of this metabolic interaction negatively affects the stability of neural networks and cognitive performance [42]. Taken together, these data show that neuroimmune mechanisms form an integrative regulatory system that ensures the structural restructuring of synapses, the preservation of cognitive functions, and the adaptation of the central nervous system to changing conditions.

Stress, systemic inflammation and their effect on the regulatory mechanisms of the central nervous system

In modern physiology, stress and systemic inflammation are interpreted as interrelated biological processes in which social and physical environmental influences are transformed into neuroimmune signals that modulate the regulatory mechanisms of the central nervous system and the functional state of the brain [13]. Research data show that chronic stress effects are not limited to psychological reactions, but are accompanied by sustained activation of innate immunity and increased levels of pro-inflammatory cytokines [33]. It is systemic inflammation that becomes the mediator through which stress affects neural networks, modulating plasticity, neurogenesis, and cognitive functions.

Despite a large number of studies, there are still disagreements about which types of stressors most significantly activate inflammatory mechanisms and how individual psychological characteristics determine the severity of the neuroimmune response [39]. Within the framework of the neuroimmune approach, stress should be considered not as a universal factor, but as a set of effects that differ in their ability to trigger pro-inflammatory signaling cascades and alter the regulation of the central nervous system. Social threats, including isolation, conflict, and loss of support, play a special role, as they activate brain networks for assessing social security and initiate pre-inflammatory reactions [45].

Historically, ideas about stress were formed within the framework of the concept of a non-specific reaction of the body, however, modern data indicate the selectivity of biological responses [47]. Activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis leads to the release of catecholamines and glucocorticoids, which directly regulate the expression of immune genes. The activity of transcription factors, including NF- κ B, is modulated through beta-adrenergic receptors and glucocorticoid mechanisms, which enhances the synthesis of IL-1b, IL-6 and TNF- α . These mediators are able to enter the brain humorally, activate the afferent fibers of the vagus nerve, or act through meningeal lymphatic structures [8].

As a result, a neuroinflammatory environment is formed that affects synaptic transmission, the balance of excitation and inhibition, and the stability of neural networks [5]. The data systematized in Table 2 demonstrate that different components of the stress response modulate immune and neuronal parameters in different ways, determining the severity of cognitive and behavioral changes. Under short-term stress, the inflammatory response can be adaptive, contributing to resource mobilization. However, with chronic exposure, a state of low-intensity systemic inflammation develops, associated with dysregulation of glutamatergic transmission and decreased neurotrophic support.

Table 2: Neuroimmune mechanisms of the influence of stress and systemic inflammation on the regulation of the central nervous system

The stress response component	Activation mechanism	Immune effects	Effects on the regulatory mechanisms of the central nervous system	Functional and clinical consequences
Psychosocial stress	Activation of limbic structures (amygdala, hypothalamus), threat signal formation	Increased production of IL-1b, IL-6, TNF- α ; activation of innate immunity	Changing the balance of arousal and inhibition, reducing neuroplasticity	Cognitive impairment, emotional dysregulation
Sympathetic Nervous System (SNS)	The release of norepinephrine and adrenaline into the blood and lymphoid organs	Activation of NF-kB, increased transcription of proinflammatory genes	Formation of a neuroinflammatory environment	Increased risk of affective and anxiety disorders
Hypothalamic–Pituitary–Adrenal axis (HPA)	Cortisol secretion in response to stress	Modulation of cytokine expression; possible glucocorticoid resistance	Violation of adaptive regulation of neural networks	Dysregulation of stress response, decreased resistance to stress
Systemic chronic inflammation	Activation of PRR, TLR, and NF-kB signaling cascades via DAMP and PAMP	Steady increase in circulating proinflammatory mediators	Disruption of synaptic transmission and neurogenesis	Decreased memory and executive functions
Microglial activation	Cytokine-induced activation of NFkB in CNS resident macrophages	Secretion of IL-1b, TNF- α , IL-6, and chemokines	Synapse remodeling, increased neuroinflammation	Neurodegenerative changes, cognitive deficits
Astrocytic dysfunction	Activation of inflammatory signaling pathways, impaired metabolic support	Excessive secretion of glutamate, changes in lactate metabolism	Extrasynaptic hyperactivation of receptors, impaired plasticity	, Neural network dysfunction, behavioral disorders
Vagus nerve	Cholinergic antiinflammatory regulation via $\alpha 7$ -nAChR	Decreased production of proinflammatory cytokines	Stabilization of neural network activity	Reducing the severity of neuroinflammatory reactions

The NF-kB signaling pathway, activated by both pro-inflammatory cytokines and molecular damage patterns, plays a key role in these processes. The canonical NF-kB pathway is rapidly activated in response to stress stimuli and promotes the transcription of inflammatory response genes, whereas the non-canonical pathway generates longer-lasting changes in

immune regulation. In CNS cells, activation of NF- κ B in microglia and astrocytes is accompanied by increased cytokine synthesis and changes in neurotransmitter metabolism [9]. Disruption of the fine regulation of these mechanisms leads to an imbalance between the protective and damaging effects of inflammation. In conditions of persistent systemic inflammation, neuroplasticity suffers, neurogenesis is inhibited, and prerequisites for cognitive disorders and affective pathology are formed [11]. Thus, stress and systemic inflammation should be considered as key factors modifying the regulatory mechanisms of the central nervous system through a complex network of neuroimmune interactions connecting the peripheral immune system and central neuronal structures.

The boundaries of the physiological norm: the transition of adaptive neuroimmune reactions to pathological ones

The idea of the boundaries of the physiological norm in the central nervous system requires consideration of the nervous system as a dynamic structure in which adaptive neuroimmune reactions maintain stability, but under certain conditions they can turn into pathological forms. Volkov A.I., Melnikov M.V. and Boyko A.N. (2021) emphasize that the protection of the brain from autoimmune inflammation is based on multilevel barrier and immunoregulatory mechanisms that limit the excessive activation of innate and adaptive immunity. The authors showed that the preservation of the blood-brain barrier, control of antigen presentation, and local production of anti-inflammatory cytokines form the functional boundary that separates the adaptive response from autoimmune damage.

Disruption of these mechanisms leads to a shift in the regulatory balance and transformation of the physiological neuroimmune response into chronic inflammation. Normally, microglia and astrocytes are involved in maintaining synaptic plasticity by regulating the density of contacts and the metabolic supply of neurons [12]. However, with prolonged stimulation by pro-inflammatory signals, their functional state changes, reflecting the transition of adaptive neuroimmune reactions to pathological ones. Verkhatsky A. and co-authors. (2023) demonstrated that astrocytes in CNS diseases lose some of their homeostatic functions and acquire properties that promote neuroinflammation and disruption of intercellular interactions.

The authors consider astroglia as a key element determining the outcome of neuroimmune activation, from neuroprotection to neurodegeneration. Physiologically, adaptive activation of glia is necessary to remove damaged structures and limit infection. Nevertheless, while maintaining the pro-inflammatory microenvironment, the expression of mediators supporting closed inflammatory circuits increases. It is at this point that the boundaries of the physiological norm become blurred, and compensatory reactions lose their reversibility. The work of Volkov et al. He focuses on the importance of immunological tolerance and suppression mechanisms that prevent autoaggression in brain tissues. The contribution of Verkhatsky and colleagues is to systematize data on glial plasticity and its role in the transition from a homeostatic state to sustained neuroinflammatory activation.

Taken together, these studies confirm that neuroimmune regulation has clear functional limits determined by the balance of pro- and anti-inflammatory signals [15]. When this balance is disrupted, adaptive responses cease to perform a protective function and become a source of damage to neural networks. Despite the accumulated data on the molecular mechanisms of glial activation and cytokine signaling, it remains unclear which quantitative and temporal parameters should be considered critical for the transition to a pathological state [19]. There are no unified physiological criteria that can objectively determine the moment of loss of reversibility of a neuroimmune reaction. The systemic markers of early regulatory imbalance have not been sufficiently studied, which makes it difficult to develop preventive strategies. These unresolved issues require the integration of molecular, cellular, and functional data within a single dynamic model [22]. In this regard, there is a need to move from a descriptive analysis of individual mechanisms to their conceptual generalization, which makes it possible to determine the system parameters that outline the boundaries of the physiological norm. This approach involves the formation of a model capable of linking molecular processes with the functional reversibility of neuroimmune activation.

The conceptual model of the boundary of the physiological norm

The accumulated data suggest that microglia are involved in the formation of synaptic and behavioral changes during chronic stress, and within the framework of the proposed conceptual model of the boundary of the physiological norm, such effects should be considered as a result of a shift in the regulatory threshold of neuroimmune activation. At the same time, there remains a need to revise the theoretical foundations combining immunological and stress-related studies, since without a clear definition of the boundaries of the norm, it is difficult to distinguish between adaptive and pathological conditions [24].

Terminology borrowed from the study of peripheral macrophages in infection turns out to be methodologically limited for describing microglia under chronic stress, where the intensity and duration of the signal do not reach classical inflammatory values. The frequent use of the term "neuroinflammation" in relation to stress-induced changes blurs the boundary of the physiological norm and creates the impression of mandatory tissue damage, which is not always true [27]. From the perspective of the conceptual model, it is more correct to consider such states as variations within the adaptive range if the mechanisms of suppression and feedback remain functionally intact. The proposed model can be represented as a system of three interrelated coordinates, including the amplitude of the neuroimmune signal, its temporal extent and the effectiveness of negative feedback mechanisms. Fluctuations of each of these parameters are allowed within the limits of the physiological norm, but their consistency ensures that the process remains reversible [29]. A violation of the proportional relationship between them forms a state of regulatory tension, which precedes the transition to stable pathological activation.

This is especially important, given that preclinical stress models are widely used to interpret the pathogenesis of mental disorders and require precise determination of thresholds for the transition to pathology. A reductionist interpretation of microglial activity without taking into account the parameters of intensity, duration, and regulatory compensation can lead to the formation of therapeutic strategies that do not take into account the physiological role of glia [30]. Modern methods, including single-core and single-cell RNA sequencing, demonstrate the heterogeneity of microglial phenotypes, which confirms the existence of a dynamic spectrum of states rather than a binary division into "rest" and "activation". This makes it possible to interpret microglial changes in different models as quantitative shifts within the regulatory range, rather than as an unambiguous departure from it. The transition to a pathological state occurs at a time when compensatory mechanisms, including suppression of proinflammatory transcriptional activity, restriction of cytokine amplification, and restoration of cellular metabolism, are insufficient to return the system to its original level [32]. In this case, positive feedback loops are formed that support activation regardless of the primary stimulus. It is the consolidation of these self-sustaining contours that indicates the crossing of the boundary of the physiological norm.

In inflammatory contexts, such as multiple sclerosis or experimental autoimmune encephalomyelitis, there is indeed an excess of threshold signal parameters with the formation of self-sustaining cytokine circuits. However, even under these conditions, microglia perform a dual function, combining cytotoxic effects with support for reparative processes, which indicates a complex structure of the regulatory boundary [5]. A similar ambivalence is found in ischemic stroke, where the outcome is determined by the balance between destructive and regenerative mechanisms, and therefore by the degree of preservation of the suppressor pathways.

In contrast to the traditional dichotomous scheme, which contrasts homeostasis and inflammation as qualitatively different states, the proposed concept considers neuroimmune regulation as a continuous dynamic spectrum [40]. In this logic, the key is not the fact of glial cell activation itself, but the ability of the system to complete the adaptive cycle and restore the initial parameters of regulation [42]. Consequently, the conceptual model of the boundary of the physiological norm allows us to consider neuroimmune reactions as a continuum of states in which the pathological process develops not as a result of activation itself, but as a result of the loss of the system's ability to return to its original homeostatic level.

Integrative aspects of neuroimmune regulation: systemic adaptation and prospects for further research

An integrative approach to neuroimmune regulation allows us to consider the central nervous system as a complex multilevel system where nervous and immune elements function in close interrelation, forming a coordinated adaptive network that supports the stability and plasticity of brain processes. Within the brain, T cells and macrophages perform not only protective but also regulatory functions, maintaining a dynamic balance between immune surveillance and maintaining neural integrity [44]. Under physiological conditions, their activity is limited and coordinated with the signals of glia and neurons, which allows maintaining tissue homeostasis without excessive inflammation. Under pathological influences, these cells are involved in multilevel cascades of interactions, where protective mechanisms can turn into damaging ones, reflecting the limits of systemic adaptation [46].

Regulatory T cells form an anti-inflammatory control circuit, secreting IL-10 and TGF- β and thereby stabilizing the neural environment. At the same time, effector subtypes, including Th1 and Th2, exhibit functional polarization, which determines the direction of the immune response and its effect on synaptic activity [48]. Through interaction with antigenpresenting cells, T cells are involved in processes affecting not only immunity, but also neuroplasticity. This emphasizes that neuroimmune regulation is not limited to inflammation, but covers the mechanisms of structural and functional restructuring of neural networks [50].

Macrophages and microglia form another key level of integration, responding to changes in the cytokine environment and damage signals. Their phenotypic plasticity reflects the system's ability to switch between pro- and anti-inflammatory programs. However, with prolonged stimulation, there is a risk of chronic inflammation, which indicates the need for precise regulation of these transitions [52]. In this context, the prospects for further research are related to the identification of molecular nodes that control the reversibility of activation. An important component of integrative regulation is the extracellular matrix, which not only provides structural support, but also modulates the migration and activation of immune cells. Its remodeling in case of damage creates conditions for repair, but in case of imbalance it helps to maintain the inflammatory background. The cytokine network distributed between microglia, astrocytes, neurons, and endothelium functions as a flexible feedback system. Low physiological concentrations of TNF- α , IL-6, and IFN- γ are involved in the regulation of synaptic transmission, while their overexpression disrupts cognitive processes [53].

Neurotrophic factors, including BDNF, GDNF, and IGF-1, link immune signals to mechanisms of neuron survival and plasticity. Their expression changes under the influence of inflammation, reflecting the close association of immune and trophic pathways. Neurotransmitters, in turn, modulate the activity of immune cells, forming a two-way communication between the electrical and immune dynamics of the brain [60]. Thus, the systemic adaptation of the central nervous system is determined by a complex balance between neurotransmitter, cytokine, and trophic signals. Historical studies of fever and activation of the hypothalamus–pituitary–adrenal axis have shown that immune signals are capable of triggering neuroendocrine feedback loops. These mechanisms demonstrate how peripheral inflammation is transformed into centralized regulatory responses [61]. Behavioral changes in the disease, including decreased motivation and cognitive flexibility, illustrate that neuroimmune processes affect higher levels of behavior organization.

Taken together, the data suggest that neuroimmune regulation is an integrative system of multilevel adaptation. Understanding its systemic principles and the limits of plasticity opens up prospects for the development of therapeutic strategies aimed at restoring the balance between protection, plasticity and cognitive function of the brain.

CONCLUSION

The presented review certainly does not pretend to provide exhaustive coverage of all aspects of the neuroimmune regulation of central nervous system functions. The work focused on the cellular and molecular mechanisms of interaction between neurons, microglia, astrocytes and the vascular component, as well as on the analysis of the boundaries of the physiological norm of neuroimmune reactions. At the same time, some areas remained outside the scope of detailed consideration, including the influence of the intestinal microbiota, circadian regulation, and age-related changes on neuroimmune dynamics, which have been actively discussed in the scientific literature in recent years.

The generalized data demonstrate that neuroimmune regulation is a multilevel system in which immune signals are not opposed to neurophysiological processes, but are embedded in mechanisms of plasticity, adaptation, and maintenance of homeostasis. Microglia and astrocytes act not only as effectors of inflammation, but also as key participants in synaptic remodeling, metabolic support, and regulation of neural network activity. A balance between pro-inflammatory and anti-inflammatory signals is essential, which determines the reversibility of activation and prevents its chronization. Disruption of this balance leads to a shift in adaptive responses towards sustained neuroinflammation, which underlies a number of neurodegenerative and cognitive disorders.

A special place in the system of neuroimmune regulation is occupied by molecular nodes, including NF- κ B, JAK/STAT-dependent mechanisms, cytokine and chemokine signaling pathways, which determine the nature of the cellular response. With physiological activation, these cascades provide protection and recovery, but with prolonged stimulation they form stable pathological contours. In this context, the problem of the boundaries of the physiological norm is reduced to clarifying the criteria for the reversibility of neuroimmune activation and identifying the mechanisms limiting the transition of an adaptive response to chronic inflammation.

A promising area of further research is the search for molecular markers of early neuroimmune balance shift, as well as the analysis of the ratio of the level of mediators and the receptor sensitivity of target cells. Probably, as in other regulatory systems of the body, not only the absolute concentration of cytokines or hormones is crucial, but also the state of the receptor apparatus, intracellular signaling pathways and epigenetic regulation. The study of these parameters can contribute to the formation of more accurate ideas about the limits of the physiological adaptation of the central nervous system.

Along with the molecular mechanisms, special attention should be paid to the systemic integration of neuroimmune, neuroendocrine, and behavioral responses. Studying the interaction of stress, metabolic, and inflammatory factors will allow for a deeper understanding of individual differences in resistance to damaging effects. In the future, this creates the basis for the development of regulatory-oriented therapeutic strategies aimed not only at suppressing inflammation, but also at restoring the physiological balance of neuroimmune communication.

Thus, the neuroimmune regulation of the functions of the central nervous system should be considered as an integrative adaptation mechanism that determines the stability, plasticity and functional integrity of the brain. Understanding its systemic principles and the limits of the physiological norm is of fundamental importance for modern physiology and opens up new opportunities for personalized approaches to the prevention and correction of neurodegenerative and stress-induced disorders.

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Contribution of the authors

The authors have made an equal and significant contribution to the collection of empirical data, their processing and the writing of the article.

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