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REVIEW

Modulating Effect of Cytokines on Mechanisms of Synaptic Plasticity in the Brain

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Abstract—After accumulation of data showing that resident brain cells (neurons, astrocytes, and microglia) produce mediators of the immune system, such as cytokines and their receptors under normal physiological conditions, a critical need emerged for investigating the role of these mediators in cognitive processes. The major problem for understanding the functional role of cytokines in the mechanisms of synaptic plasticity, *de novo* neurogenesis, and learning and memory is the small number of investigated cytokines. Existing concepts are based on data from just three proinflammatory cytokines: interleukin-1 beta, interleukin-6, and tumor necrosis factor-alpha. The amount of information in the literature on the functional role of antiinflammatory cytokines in the mechanisms of synaptic plasticity and cognitive functions of mature mammalian brain is dismally low. However, they are of principle importance for understanding the mechanisms of local information processing in the brain, since they modulate the activity of individual cells and local neural networks, being able to reconstruct the processes of synaptic plasticity and intercellular communication, in general, depending on the local ratio of the levels of different cytokines in certain areas of the brain. Understanding the functional role of cytokines in cellular mechanisms of information processing and storage in the brain would allow developing preventive and therapeutic means for the treatment of neuropathologies related to impairment of these mechanisms.

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Contemporary studies indicate that resident brain cells produce such immune system neuromediators as the cytokines, and both systems (nervous and immune) exhibit similar mechanisms of intercellular communications [1, 2]. Traditionally, the cellular mechanisms of information processing and storage in the brain were considered regarding solely neuronal interactions. Later, it became clear that the cellular and molecular mechanisms of brain cognitive functions cannot be understood without accounting for the involvement of glial cells into these interactions. Subsequently, the role of astrocytes in such interactions came into focus. Relatively recently, upon understanding that neurons, astrocytes, and microglia produce cytokines and their receptors able to modulate synaptic plasticity, as well as the processes of learning and memory under normal physiologic conditions [3, 4], an urgent demand emerged for studying the role of these mediators in cognitive processes.

The cytokines are endogenous peptide immunomodulators, and their function is related to the activation of immune system cells as a response of the organism to inflammation, differentiation of cells, and cell death and survival in response to damaging factors [5]. Over a number of years, it became recognized that immune system mediators provide virtually no effect on the activity of brain cells under normal physiological conditions, alter-

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole; BDNF, brain-derived neurotrophic factor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; CNS, central nervous system; CREB, cAMP response element-binding protein; Erk/MAPK, signaling pathway; GABA, γ-aminobutyric acid; GluA1 and GluA2, subunits of AMPA receptors; IKK, IκB kinase complex; IL-1, interleukin-1; IL-1ra, interleukin-1 receptor antagonist; IL-1RI and IL-1RII, interleukin-1 receptors; IL-6, interleukin-6; JAK/STAT, JAK kinase and signal transducers and activators of transcription; LSD, long-term synaptic depression; LSP, long-term synaptic potentiation; MHC-1, major histocompatibility complex I; NF-κB, nuclear factor kappa B; NMDA receptors, N-methyl-D-aspartate receptors; Rab3, small GTP-binding protein; RhoA, small G-proteins; RIM proteins, Rab3-interacting molecules; SB_{431542}, inhibitor of TGFβ; TGFβ, transforming growth factor beta; TNF, tumor necrosis factor; TNFR1 and TNFR2, TNF receptors; TTX, tetrodotoxin.

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ing this activity only in neuropathologies due to the disruption of the brain–blood barrier permeability. However, in recent years novel experimental data indicated that along with participation in neuropathological immune and inflammatory processes [6, 7], cytokines play a crucial role in synaptic plasticity, *de novo* neurogenesis, and the processes of learning and memory under normal physiological conditions [3, 4].

The functioning of the central and peripheral nervous systems is mediated by two opposite requirements: on the one hand – by a demand for change in structural and functional properties, on the other hand by the necessity for stabilization of these properties [8]. Analysis of data in the literature shows that neuronal networks are characterized by long-term alterations in the number of synaptic connections and the efficiency of synaptic transmission determined by the level of neuronal activity. It is presumed that long-term potentiation of synaptic transmission in brain neurons underlies the cellular/molecular mechanisms of learning and memory [9]. On the other hand, homeostatic plasticity enables stabilization of functioning of the neuronal network [10, 11].

The main scope of this review is the analysis of available information on the modulating effects of pro- and antiinflammatory cytokines on such types of long-term synaptic plasticity as Hebbian synaptic plasticity and homeostatic synaptic plasticity in the brain of mature animals. Additionally, signaling pathways promoting the modulating effects of cytokines are investigated, along with effector target proteins of excitatory and inhibitory synaptic transmission, through which the studied cytokines mediate these effects on various forms of synaptic plasticity and the processes of learning and memory.

HEBBIAN PLASTICITY

Synaptic plasticity is a property of specific interneuronal connections (synapses) determining their ability to alter the efficiency of signal transmission from one neuron to another depending from the type of their preceding activation [9, 12-15]. Importantly, the duration of synaptic transmission change can significantly exceed the period of the modulating action itself.

In 1949, D. Hebb proposed a form of synaptic plasticity according to which the matching of activities of pre- and postsynaptic neurons is accompanied by a prolonged enhancement of the efficiency of synaptic transmission. Later, this type of plasticity was named "Hebbian plasticity". According to modern assumptions widely accepted among neurobiologists, Hebbian plasticity accounts for the cellular mechanisms of the development of memory.

In the 1970s and 1980s, experiments in hippocampal neurons indicated that such increase in synaptic transmission efficiency indeed takes place in certain synapses in the brain. An opposite process of reduction of this efficiency in the absence of correlation between the activities of pre- and postsynaptic neurons was also determined. These Hebbian forms of synaptic plasticity were named long-term synaptic potentiation (LSP) and long-term synaptic depression (LSD), respectively [12, 16, 17]. In experiments with hippocampus slices, LSP is often induced by high-frequency stimulation of Schaffer collaterals, consisting of a single or a set of electric impulses of 50-100 Hz over 1 sec. The protocol of LSD includes a series of low-frequency impulses (1-3 Hz) over 5-15 min. There are numerous forms of long-term synaptic plasticity mediated by different cellular/molecular mechanisms [18]. The best-studied type of LSP depends on NMDA glutamate receptors in the CA1 hippocampus field. It was established that LSP induction in CA1 of the hippocampus requires activation of NMDA receptors during strong postsynaptic depolarization, leading to an increase in calcium ion concentration in the postsynaptic neuron. Transduction of this calcium signal is mediated by various intracellular signaling pathways that involve Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), Erk/MAPK-signaling pathway and an atypical form of protein kinase C – PKMζ. This form of LSP is characterized by postsynaptic expression mechanisms conditioned by changes in the properties and number of AMPA receptors integrated into postsynaptic densities [19-25].

Contemporary experimental data indicate that LSP is associated with integration of a higher number of AMPA receptors in the postsynaptic membrane, whereas LSD is mediated by removal or endocytosis of synaptic AMPA receptors [26]. The mechanisms for maintaining LSP dependent from NMDA glutamate receptors *in vitro* consist of at least two phases: an early phase lasting 30-60 min, and a late phase of 1-2 h. The late phase of this form of LSP *in vivo* can last for weeks and even months [27]. The mechanisms underlying the maintenance of these phases are diverse, being determined by cascading intracellular signaling pathways including PKA, CaMKIV, and Erk/MAPK kinases, transcription factors (c-Fos, Zif268/Egr-1) and expression of effector genes and growth factors regulating the formation of neuronal branches and new synapses (BDNF) [21, 22, 28].

A review by Raymond [27] discusses evidence that the induction of different phases of LSP is associated with selective involvement of the following mechanisms. Induction of early LSP phase is selectively dependent on the signaling within the dendritic spine. A single episode of conditioning stimulation leads to an influx of Ca^{2+} through NMDA receptors, which in turn results in ryanodine-dependent Ca^{2+}-induced release of Ca^{2+} from the endoplasmic reticulum of the neuron, which provides a local activation of CaMKII in the postsynaptic density. Phosphorylation of specific synaptic proteins, such as

AMPA receptors, leads to LSP induction, which is concluded after approximately 1-2 h. The late phase of LSP is mediated by the activation of group I mGlu receptors, which is activated synergistically with NMDA receptors and induces inositol triphosphate-dependent Ca^{2+} release from neuronal endoplasmic reticulum. In addition, mGlu receptors induce the formation of diacylglycerol, which in combination with Ca^{2+} activates local protein synthesis in dendrites through PKC and ERK protein kinases. Moreover, another signaling cascade involving PI3 kinase and mTOR can also contribute to local protein synthesis in the dendrite. Proteins regulated in synthesis by this signaling pathway provide longer maintenance of LSP. Repetition of the conditioning stimulation results in an additional influx of Ca^{2+} through L-type voltage-gated calcium channels and induction of gene transcription. This transcription may be induced by either Ca^{2+} *per se* or in complex with calmodulin.

Additional neuromodulatory signals for gene transcription can act via dopaminergic synaptic inputs and D_5 receptors activating protein kinase A, which in turn regulates the activity of cAMP response element (CRE)-binding protein (CREB). Relatively recently, a novel class of noncoding microRNAs involved in local mRNA translation in synapses and regulating plasticity was reported [29]. In the hippocampus, the brain-specific microRNA mir-134 inhibits the translation of proteins localized in the synaptodendritic compartment of neurons, where they reduce the size of dendritic spines through the repressive effect of LIM kinase (Lim k1).

HOMEOSTATIC PLASTICITY

It should be mentioned that Hebbian synaptic plasticity is realized with the involvement of a positive feedback mechanism that can destabilize the activity of neurons in a local neural network. Therefore, to maintain the efficiency of synapses and their plasticity at an optimum level, certain mechanisms must exist for the regulation of synapse-specific LSP or LSD, both at the cellular level and at the level of the local neural network [30]. Such a mechanism not related to Hebbian plasticity was indeed discovered and named "homeostatic synaptic plasticity" [8, 30, 31]. Unlike Hebbian plasticity, homeostatic plasticity functions with the implication of a negative feedback mechanism and is conditioned by changes in the efficiency of all synapses in a certain neuron, rather than of an individual synapse of this neuron [10, 31]. During prolonged periods of neuronal hyperactivity or lack of activity, homeostatic plasticity tends to maintain and stabilize an optimal level of activity, facilitating the implementation of Hebbian synaptic plasticity and, possibly, formation of memory and learning ability of animals, including humans [10, 11].

Recent studies conducted both *in vivo* and using organotypic neuron cultures demonstrated that in homeostatic synaptic plasticity the synaptic scaling is not always uniform, and alterations in the activity of a local neuronal network are not equivalent in their effect on all the synaptic inputs of a given neuron [18, 30, 32]. For instance, chronic injection of tetrodotoxin (TTX) in a culture of hippocampal neurons raises the transmission efficiency in CA3–CA1 synapses, while synaptic inputs of neurons from the CA3 field are regulated differently: recurrent CA3–CA3 inputs are weakened, whereas the connections between mossy fibers and CA3 neurons become more efficient. In TTX-treated neocortical cell culture, the performance of inhibitory synaptic inputs from parvalbumin-positive inhibitory neurons to excitatory neurons decreases, while their efficiency from somatostatin-positive inhibitory neurons does not change [33]. According to Pozo and Goda [30], brain-derived neurotrophic factor (BDNF) serves as a coordinator between Hebbian and homeostatic types of synaptic plasticity, and the mechanisms of homeostatic plasticity are implemented both at pre- and postsynaptic levels. It is assumed that reduced neuronal activity (upon chronic effect of TTX) leads to increased recycling of synaptic vesicles, enhanced merging of vesicles with the presynaptic membrane, and the probability of release of neurotransmitter at presynaptic level. At postsynaptic level, the integration of neurotransmitter receptors into the synapse is increased due to their lateral diffusion from the intracellular pool.

After the original studies that demonstrated the existence of homeostatic plasticity in chronic modulation of neuronal activity, most studies aimed at investigating the role of AMPA glutamate receptors in excitatory synapses in implementing the mechanisms of this plasticity. Analysis of these works showed that chronic deprivation of activity is attended by the integration of newly synthesized AMPA receptors as homotetramers composed of solely GluA1 subunits or of heterotetramers of GluA1 and GluA2 subunits [34, 35].

Homeostatic plasticity only in excitatory synapses is insufficient for maintaining the stability of a local neural network [31]. For instance, cortical neural networks exhibit intensive positive feedback loops between excitatory pyramidal neurons controlled by the mechanisms of direct and recurrent inhibition. Slight alterations in the balance between excitation and inhibition in such neural networks can disturb the cortical functions and the induction of Hebbian synaptic plasticity. Similarly to homeostatic plasticity, inhibition in excitatory synapses is modified through alterations of amplitude of the released neurotransmitter quanta and clustering of postsynaptic receptors. However, reduction in the number of functional inhibitory synapses is also observed. Excitatory and inhibitory synapses in cultured cortical neurons are regulated in opposite directions. However, GABAergic

interneurons are highly diverse and play different roles in the functioning of cortical micronetworks. This raises a question: are all inhibitory synapses regulated by the same homeostatic mechanisms, or do various functional classes of inhibitory interneurons give different responses to long-term changes in their activity?

One of the key issues is the question of the mechanisms of interaction between the Hebbian and homeostatic forms of synaptic plasticity [10]. Notably, some forms of homeostatic plasticity are fast-developing (comparable to Hebbian plasticity). One possible scenario was hypothesized by Rabinowitch and Segev [36]. According to their hypothesis, Hebbian plasticity in a single synapse is balanced by the changes in the efficacy of neighboring synapses.

Modern investigations on rat cerebellum showed that this event can indeed take place [37]. Another way of interaction between Hebbian and homeostatic plasticities was discovered in studies on the hippocampus [38]. Chronic suppression of neural activity by TTX in hippocampal excitatory CA3–CA1 synapses increases signal transmission efficiency through the involvement of additional AMPA glutamate receptors. It was surprising to find that LSP in these synapses was manifested following induction of homeostatic synaptic plasticity. Moreover, a more pronounced LSP was observed in the case when the effect of TTX has covered the synapses containing only NMDA glutamate receptors. Such synapses gave no response on basal glutamate release and remained "silent" under basal conditions. Induction of LSP activated these "silent" synapses via integration of AMPA receptors in postsynapses. The authors of this work presumed [38] RIM (Rab3-intercating molecules) proteins that interact with presynaptic channels, as well as with Rab3 proteins, to be key regulators of homeostatic plasticity at the presynaptic level. Adaptation to chronic inactivation results in an increase in RIM-dependent Ca^{2+} influx in the presynaptic terminal and RIM/Rab3-dependent interaction of synaptic vesicles with the presynaptic membrane, increasing the probability of a pool of synaptic vesicles available for release. At postsynaptic level, chronic inactivation increases postsynaptic efficiency of signal transmission through integration of additional AMPA glutamate receptors in neuronal postsynaptic densities.

According to some researchers, a higher order form of synaptic plasticity also exists, along with Hebbian and homeostatic plasticities, which was named "metaplasticity" [15]. Metaplasticity is the "plasticity of plasticity". The best-studied example of metaplasticity is observed when the preceding activity shifts the induction threshold of LSP and LSD. Thus, in the hippocampus, repetitive activation of NMDA receptors, which itself does not induce LSP or LSD, may still cause a rapid shift of thresholds, which leads to difficult activation of LSP and easier activation of LSD.

MODULATING EFFECT OF CYTOKINES ON SYNAPTIC PLASTICITY

Present data indicate that such proinflammatory cytokines as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are involved in the processes of learning and memory [11]. However, modulation of memory processes caused by these cytokines is a complex phenomenon including both facilitating and damaging effects depending on the specific proinflammatory cytokine, its levels in the brain, and specific conditions for its release [39]. These results were obtained in experiments on the hippocampus upon studying such forms of memory as declarative memory in humans and spatial or contextual memory in animals.

A review of Pribiag and Stellwagen [40] provides data about the impact of neuroimmune molecules that are constitutively expressed in the brain, such as TNF-α, major histocompatibility complex I (MHC-1), and neuronal pentraxins, which mark cells for subsequent degradation and phagocytosis. MHC-1 molecules play an important role in the homeostatic regulation of synaptic function. It is known that MHC-1 complex is polygenic, consisting of a heavy α-chain associated with an invariant light β2 chain of microglobulin β2m. In addition, surface expression MHC-1 requires transport complex TAP1 (transporter associated with antigen processing 1). Several-day culturing with TTX of dissociated hippocampal neurons from mice with β2m/TAP1 knockout disturbed the development of homeostatic synaptic plasticity in these neurons. Interestingly, deficiency of MHC-1 signaling, in contrast to homeostatic plasticity, increased Hebbian plasticity. Homeostatic response was also absent in a culture of neurons from *Narp*$^{-/-}$ knockout mice (Narp – pentraxin modulated by neuronal activity). The authors also point out that such proinflammatory cytokines as TNF-α, IL-1β, and IL-6 activate excitatory and suppress inhibitory synaptic transmissions in ways that resemble the development of homeostatic synaptic plasticity. Notably, TNF-α signaling is not involved in Hebbian plasticity.

Data obtained to date suggest that modulation of learning and memory caused by proinflammatory cytokines is likely mediated by their effects on different forms of synaptic plasticity [11, 41]. Summarizing the results described in the literature, it can be concluded that physiological level of IL-1 in the brain is necessary for the induction of Hebbian LSP, whereas pharmacological inhibition of IL-1 signaling pathways or knockout of the IL-1-coding gene leads to elimination of LSP induction. On the other hand, such experiments revealed that IL-6 plays an important role in the completion of LSP.

Under physiological conditions, the level of IL-6 in the central nervous system (CNS) is low. However, clini-

cal trials demonstrated a significant increase in IL-6 in different brain structures in patients with schizophrenia, Alzheimer's disease, ischemic stroke, and convulsion [42]. Using isolated slices of rat hippocampus, it has been demonstrated that application of exogenous IL-6 eliminated the development of LSP in CA1 pyramidal neurons [43]. The authors showed that this action of IL-6 on LSP was associated with prolonged increase in the level of the phosphorylated active form of STAT3 protein and reduced activity of p44/42 MAPK kinase. The effect of IL-6 was also abolished by inhibitors of JAK2 kinase.

Compelling data were obtained by a group of researchers under the supervision of Malenka regarding the role of TNF-α in synaptic plasticity. According to their results, the signaling pathway activated by this proinflammatory cytokine is essential for implementation of homeostatic synaptic plasticity dependent on the previous experience (synaptic scaling process) [44, 45].

These investigators showed that acting through TNF-α receptor 1, TNF-α provides an increase in the integration of AMPA glutamate receptor isoforms lacking GluA2 subunits in the plasma membrane (that leads to enhanced Ca^{2+} conductivity). In pyramidal hippocampal neurons, this process is regulated through a phosphatidylinositol 3-kinase-dependent signaling pathway.

It has been revealed that TNF-α additionally reduces incorporation of $GABA_A$ receptors into the plasma membrane of the same neurons, thus lowering the efficiency of inhibitory synaptic transmission [11]. Hence, TNF-α can regulate local homeostasis of a hippocampal neural network towards intensification of excitatory processes, which may result in damaging of hippocampal neurons. McAffose and Baune [11] assume the following scheme of TNF-α-mediated molecular mechanisms and neuron–glia interactions, modulating synaptic plasticity and processes of learning and memory in normal brain. Under normal physiological conditions, astrocytes play a central role in synaptic integration and neuronal processes. In particular, release of TNF-α from astrocytes during prolonged synaptic activity causes simultaneous activation of several processes, such as (i) activation of small G proteins (RhoA) and, via their action, long-term regulation of dendrite branching and synaptogenesis; (ii) increase in the number of AMPA receptors in the postsynaptic membrane and enhancement of the efficiency of excitatory synaptic transmission mediated through type-1 TNF-α receptor and PI3 kinase; (iii) activation of type-1 TNF-α receptor and type-5 metabotropic glutamate receptors, leading to either inhibition of early phase Hebbian LSP (via p38 MAPK-dependent activity) or to inhibition of late phase LSP (via p38 MAPK-independent activity), and (iv) activation of nuclear transcription factor NF-κB inducing long-term depression of synaptic transmission.

Unlike proinflammatory cytokines, there are practically no data in the literature regarding the role of antiinflammatory cytokines in the mechanisms of their modulatory action on synaptic plasticity and the processes of learning and memory in the brain of mature mammals under normal physiological conditions. However, it is known that in normal brain, as well as is in neuroinflammatory processes, antiinflammatory cytokines perform an immunomodulatory role by inhibiting the production of proinflammatory cytokines and neutralizing their potentially damaging effect on brain cells [46, 47]. Under normal physiological conditions, immune mechanisms activated by environmental stimuli promote reorganization of local neural networks and facilitate memory consolidation, synaptic plasticity, and *de novo* neurogenesis. Normally, these positive effects of immune system mediators are conditioned by a complex interaction between the brain cells realizing immune functions (microglia and astrocytes) and neurons through release of classical neurotransmitters (e.g. glutamate and GABA) and production of pro- and antiinflammatory cytokines. Influenced by the action of stressful stimuli, microglia and astrocytes can produce high levels of proinflammatory cytokines and disrupt the delicate balance of cytokines required for normal processes of synaptic plasticity and memory formation at the local neuronal level and at the whole brain level. Antiinflammatory cytokines play a key role in the regulation of this balance. Thus, without investigating the fundamental mechanisms of the modulating action of antiinflammatory cytokines on synaptic plasticity and memory formation in mature mammalian brain, it is impossible to elaborate a cytokine model of realization of cognitive functions in the brain that is postulated by many neuroscience researchers [11].

However, over the last few years data have been accumulated demonstrating that such antiinflammatory cytokine as transforming growth factor-beta (TGF-β) is capable of modulating both excitatory and inhibitory synaptic transmission and affecting the growth of dendrites in mature mammalian brain [48, 49]. Moreover, experimental data indicate that addition of exogenous TGF-β1 to hippocampal slices of mice provides conversion of the early phase of Hebbian LSP into the late phase [50]. Blockade of the signaling pathway of endogenous TGF-β1 using specific inhibitor SB_{431542} broke the development of LSP and memory in animals.

Several basic directions of studies in this field of neurobiology can be mentioned: (i) investigation of the role of different cytokines (especially antiinflammatory) in the modulation mechanisms of synaptic plasticity, learning, and memory in the brain of adult mammals; (ii) studying signaling cascades through which the modulatory effects of different cytokines are mediated; (iii) analysis of target genes involved in the modulating effects of different cytokines; and (iv) studying molecular "switches" that determine neuroprotective or damaging effects of different cytokines in neuropathologies.

INVOLVEMENT OF CANONICAL AND NONCANONICAL INTRACELLULAR SIGNALING PATHWAYS IN MECHANISMS OF MODULATING EFFECTS OF CYTOKINES ON ACTIVITY OF BRAIN NEURONS

According to literature data, a canonical intracellular signaling pathway mediating the action of cytokines is associated with the activation of the JAK/STAT (Janus kinase/signal transducer and activator transcription) mechanism of signal transduction, which is involved in the mechanisms of long-term synaptic plasticity in mammals [51], and memory formation in drosophila [52]. JAKs are a family of receptor tyrosine kinases consisting of four isoforms: JAK1, JAK2, JAK3, and TYK2. They are activated by various cytokines, growth factors, and kinases acting in the regulation of transcription of many genes. Of the four JAK isoforms and seven STAT isoforms, only JAK2 and STAT3 are expressed in the brain, where they reside in postsynaptic densities. According to Nicolas et al. [51], the JAK/STAT pathway plays a significant role in the induction of NMDA-dependent long-term depression of synaptic transmission in the rat hippocampus.

As mentioned above, such antiinflammatory cytokine as TGF-β has not only neuroprotective and neurotrophic functions in the brain, but it is also able to directly modulate both excitatory and inhibiting synaptic transmission and affect the growth of dendrites in normal mature mammalian brain [48, 49]. Interestingly, such canonical TGF-β signaling pathway as TGFβ-Smad3 can differently regulate the growth of dendrites and synaptogenesis in neurons and astrocytes.

Proinflammatory cytokines IL-1 is a family of three proteins: IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1ra) [53]. These proteins are formed from precursors that are products of different genes. It has been shown that under the action of cysteine protease caspase-1 or IL-1-converting enzyme, the precursor of IL-1β is transformed into its active form [54]. Most of the active form of IL-1α remains associated with the membrane, whereas IL-1β is the secreted form of IL-1 [55]. IL-1α and IL-1β are believed to act identically by binding to plasma membrane receptor IL-1RI, which has a molecular weight of 80 kDa. Activation of this receptor leads to transduction of the signal to intracellular signaling cascades and depends on the association of the receptor with accessory proteins (AcP). The second receptor, IL-1RII, with a molecular weight of 68 kDa, also binds to IL-1, but this type of receptor is incapable of signal transduction due to the lack of domains mediating its interaction with intracellular signaling systems. IL-1ra binding to IL-1RI does not result in receptor association with auxiliary protein required for signal transduction, thus the action of IL-1α and IL-1β is blocked. Stimulation of IL-1RI receptor by IL-1 through different intracellular signaling systems may activate NF-κB (nuclear factor kappa B)-inducible kinase (NIK), subsequent phosphorylation and degradation of NF-κB inhibitor (IκB), release of NF-κB, and its translocation to the nucleus [56]. In addition, IL-1 can activate intracellular signaling cascades that involve p42/p44 mitogen-activated protein kinase (MAPK), p38 MAPK, c-Jun N-terminal kinase (JNK1) [57], and TNF/IL-1-induced protein kinase, which is activated solely by IL-1 and TNF. The activation of these signaling pathways by IL-1 was first discovered in peripheral tissue cells. It is presumed that similar signaling mechanisms that mediate the functional effects of IL-1 are also present in the cells of the central nervous system.

Data on the expression of IL-1 and its receptors in the brain lead to the following generalized conclusion. Their constitutive expression in neurons and glial cells under normal conditions is low or undetectable, depending on the brain area and type of cells, and is enhanced in response to damaging factors [4, 5]. IL-1 has diverse effects on the functional activity of the brain. In particular, at systemic level IL-1 is involved in the modulation of activities related to: (i) hormonal system: hypothalamus–hypophysis–adrenal [58], (ii) system of body temperature maintenance [59], (iii) behavioral "diseased" condition [6], and (iv) the sleep–wake cycle [60].

At the cellular level IL-1: (i) inhibits the activity of glucose-sensitive neurons of the lateral hypothalamus [2]; (ii) stimulates synthesis and release of vasopressin in neurons of the paraventricular and supraopticus nuclei of the hypothalamus [61]; (iii) reduces $GABA_A$ receptor-mediated inhibition of Purkinje cells in the cerebellum [62]; (iv) inhibits long-term potentiation of glutamatergic transmission in the hippocampus [63], and (v) inhibits calcium currents through N-type voltage-gated Ca^{2+} channels [64]. In addition, IL-1 can induce astrocyte and microglial proliferation, as well as stimulate the growth of blood vessels in the brain and increase their permeability [65].

Summarizing the available data on the possible mechanisms of neuroprotective and neurodegenerative actions of IL-1, Allan and Rothwell [5] propose that the neuroprotective effect of this cytokine may be related to its ability to block Ca^{2+} currents in neurons, inhibit glutamate release from nerve endings, inhibit long-term potentiation of synaptic transmission, and enhance inhibitory GABAergic transmission. On the other hand, mechanisms inducing neurodegeneration may also include the ability of IL-1 to stimulate the activities of cyclooxygenase 2 and the inducible form of NO synthase.

IL-1α and IL-1β associate with membrane receptor IL-1RI with the participation of auxiliary protein AcP, leading to subsequent signal transduction [5]. IL-1ra (IL-1 receptor antagonist) prevents association of IL-1RI with AcP. The formation of a complex of IL-1RI/AcP with adapter protein MyD88 activates kinases associated with IL-1RI (IRAK1 and IRAK2) followed by induction of TNFR-associated factor 6 (TRAF6). This ultimately

provokes the activation of NF-κB and MAPK signaling cascades.

Nevertheless, it appeared that IL-1β can also exert a modulating effect on the excitability of brain neurons through noncanonical signaling mechanisms. The first evidence confirming that proinflammatory cytokines can regulate neuronal membrane channels was obtained in the early 1990s, when IL-1β was shown to modulate voltage-gated Ca^{2+}-channels and $GABA_A$ receptors [66, 67]. Later it turned out that IL-1β and other proinflammatory cytokines can provide a direct modulating effect on L- and N-type voltage-gated Ca^{2+}-channels in hippocampal neurons, sodium channels in the neurons of the trigeminal nerve, and other voltage-gated channels of brain neurons [68-70]. IL-1β and IL-2 also potentiate NMDA-dependent currents, reduce the frequency of AMPA-mediated mEPSC, and modulate $GABA_A$ receptor-mediated currents in brain neurons [68].

According to some studies, the level of TNF-α in the rat brain depends on the time of day, varying, in particular, in the hippocampus from 275 pg/g protein in the morning hours to 25 pg/g of protein at night [71]. As in the case of IL-1, this increase in TNF-α expression depends on the brain region and cell type. It is assumed that the primary source of TNF-α and IL-1 in the brain is microglia. However, astrocytes and oligodendrocytes are also able to secrete TNF-α [72]. TNF-α is a peptide (17 kDa) that can bind as a multimer with two types of receptors in the brain: TNFR1 (p55) and TNFR2 (p75) [73, 74]. Receptors for TNF-α are constitutively expressed in neurons and glial cells of various brain regions, including the neocortex, hippocampus, diencephalon, hind brain, and cerebellum. TNFR1 contains an intracellular "death domain" and apparently participates in cell death. On the other hand, TNFR2 does not contain this domain, and it most likely fulfills trophic or protective function in the brain. Similarly to IL-1, the effects of TNF-α can be mediated by transcription factor NF-κB [75]. This fact indicates that IL-1- and TNF-α-induced pathways in brain cells can be integrated into common signaling cascades involving, in particular, kinases of mitogen-activated protein kinase (MAP kinase) [76].

As in the case of IL-1, TNF-α has a diverse effect on the activity of neurons in the brain. Frequently, but not always, their effects are similar. At the systemic level, TNF-α is also involved in the regulation of sleep [60], while at the cellular level TNF-α inhibits the activity of glucose-sensitive neurons of the lateral hypothalamus [2]. Additionally, TNF-α can enhance short-term outward K^+-current in a culture of cortical neurons in rats [77] and potentiate Ca^{2+}-currents and reduce glutamate-induced currents in a culture of rat hippocampal neurons [78]. The latter effects of TNF-α are mediated by transcription factor NF-κB. Similarly to IL-1, TNF-α can activate the proliferation of astrocytes and microglia, stimulate the growth of blood vessels in the brain, and increase their permeability [65]. It is presumed that TNF-α released from glial cells under normal conditions functions as a homeostatic modulator of synaptic plasticity in a local network of neurons in the brain. TNF-α was shown to increase the expression of AMPA glutamate receptors and reduce the expression of $GABA_A$ receptors in hippocampal neurons, thus regulating the potentiality for plastic changes in neural networks of this region of the brain [44, 45].

Summarizing the currently available data, proinflammatory cytokines IL-1 and TNF-α can influence the excitability of brain neurons depending on their local concentration, cell type, duration of action, and the type of receptors mediating the effects of these cytokines.

Canonical signaling pathways that mediate the activation of TNF-α are represented by two transmembrane receptors – TNFR1 and TNFR2 [5]. In particular, TNFR1 activation leads to the formation of a complex consisting of TRAF2/5, RIP1, and FADD through TRADD adaptor protein. Subsequent activation of caspase 8 induces apoptosis. TRAF2/5 and RIP1 activate NF-κB and AP-1 via the activation of IKK and MAPKs.

Just like IL-1β, TNF-α can produce a direct modulating effect on the excitability of neurons in the brain through noncanonical signaling mechanisms. Similarly to IL-1β, TNF-α modulates all the main types of potential- and ligand-dependent membrane channels in brain cells [79]. However, IL-1β modulates such currents, which are predominantly mediated by NMDA receptors, whereas TNF-α specifically interacts with AMPA receptors through TNFR1. Interestingly, TNF-α can modify extracellular glutamate level via intensification of its release from astrocytes and microglia.

The binding of the major antiinflammatory cytokine IL-10 to its membrane receptor activates three canonical intracellular signaling pathways, namely JAK/STAT, MEK/ERK, and PI3 kinase/Akt [80]. It has been shown experimentally that IL-10 can regulate the activity of PI3 kinase/Akt, MEK/ERK, and transcription factor NF-κB through stimulation of the JAK/STAT signaling pathway. This leads to the activation of genes encoding products that, on the one hand, inhibit apoptosis, and on the other hand stimulate the protective mechanisms of cells in the organism. The modulating effects of IL-10, mediated by this chain of events, are developed with high latency, requiring several hours or days for their realization. Like proinflammatory cytokines, antiinflammatory cytokines can modulate the excitability of nerve cells through ligand- and voltage-gated membrane channels. Notably, unlike canonical effects, this influence on neuronal activity can be observed in as little as several minutes following their application to the membrane of nerve cells (rapid effects) [45, 81, 82]. Our previous studies have demonstrated such antiinflammatory cytokines as IL-10 and TGF-β1 to have rapid neuroprotective action against dis-

turbances of the functional activity of brain neurons induced by hypoxia or epileptogenic stimuli [83]. The rapid modulating effects of IL-10 were mediated by noncanonical direct impact of these signaling molecules on Ca^{2+}-dependent potassium channels and blockade of inositol triphosphate-dependent release of calcium ions from the endoplasmic reticulum [84]. Our subsequent studies revealed modulating action of IL-10 on the expression of Ca^{2+}/calmodulin-dependent protein kinase II and GluA1 subunit of AMPA ionotropic glutamate receptors [85]. It is important to note that rapid modulatory effects of IL-10 are not mediated by such classic for cytokines transcription factor as NF-κB.

The principal objective of this review was to analyze the existing data on the modulating action of pro- and antiinflammatory cytokines on various forms of synaptic plasticity, such as Hebbian synaptic plasticity and homeostatic synaptic plasticity in the brain of mature animals.

The propensity for cellular memory on incoming extracellular signals is one of the vital fundamental properties of the nervous system. According to modern views, the cellular mechanisms of memory formation are underlain by various forms of Hebbian plasticity – long-term synaptic potentiation and long-term synaptic depression. Several fundamental mechanisms for maintaining different phases of long-term synaptic potentiation have been described, including various intracellular signaling pathways such as PKA, CaMKII, CaMKIV, and Erk/MAPK kinase, PI3 kinase and mTOR, transcription factors (c-Fos, Zif268/Egr-1), and BDNF.

Unlike Hebbian plasticity, which is implemented at the level of individual neuronal synapses and may eventually result in destabilization of a neuronal network, homeostatic plasticity is stipulated by changes in the efficiency of all synapses of a neuron. Regulation of homeostatic plasticity takes place both at presynaptic and postsynaptic levels. During prolonged periods of alterations in neuronal activity, homeostatic plasticity stabilizes the activity of both individual neurons and the complete local neural network, facilitates the implementation of Hebbian synaptic plasticity, and likely contributes to memory formation. However, several key issues related to the mechanisms of homeostatic synaptic plasticity remain unsolved. (1) When and how does the neuron "decide" to launch these mechanisms? (2) What are the time ranges and spatial coordinates at which homeostatic sensors detect changes in the activity level of the local neural network and redefine these values? (3) What mechanisms contribute to homeostatic synaptic plasticity?

The data currently available in the literature indicate that maintaining the balance between pro- and antiinflammatory cytokines at a certain level is required for the regulation of synaptic plasticity and memory formation in individual neurons and in the whole brain. It has been shown that the processes of learning and memory involve proinflammatory cytokines IL-1, IL-6, and TNF-α [11, 42]. The results obtained in a study related to declarative memory in humans and spatial and contextual memory in animals indicate that the modulation of memory processes mediated by these cytokines largely depends on the level of a specific cytokine in the brain, the region of the brain, and the experimental conditions promoting its release and mediating either damaging or facilitating action. The level of TNF-α in the brain also depends on the time of day [71].

It has been found that some cytokines, in particular IL-1β and TNF-α, can directly modulate the excitability of brain neurons not only via direct interaction with their receptors and subsequent activation of intracellular signaling pathways, but also through noncanonical signaling mechanisms. Unlike canonical effects, this influence on the activity of neurons can be observed in as little as several minutes after their application to the membrane of nerve cells. Both IL-1β and TNF-α modulate all the main types of voltage- and ligand-dependent membrane channels in brain cells [79]. IL-1β can affect the currents mediated by NMDA receptors, while TNF-α specifically interacts with AMPA receptors. TNF-α can also modify the level of extracellular glutamate by enhancing its release from astrocytes and microglia. Rapid modulatory effects of IL-10 on Ca^{2+}-dependent potassium channels and inositol triphosphate-dependent release of calcium ions from the endoplasmic reticulum have been revealed [84], as well as the modulating action of IL-10 on the expression of Ca^{2+}/calmodulin-dependent protein kinase II and expression of GluA1 subunit of AMPA receptors.

Based on the abovementioned findings, it can be concluded that cytokines play a significant role in the modulation of various forms of synaptic plasticity and are involved in memory formation. Beside the basic mechanism of action, the cytokines provide a modulating action through noncanonical pathways, in particular, carrying out the regulation of voltage-gated channels, glutamate receptors, GABA receptors, etc. The available experimental data are obviously insufficient for understanding the functional role of the cytokines in the regulation of neuronal activity and cognitive functions of the brain. The answers to the questions remaining will be found in future studies.

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