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Review

Nervous and immune systems signals and connections: Cytokines in hippocampus physiology and pathology

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ABSTRACT

Signaling through secretion of small molecules is a hallmark of both nervous and immune systems. The scope and influence of the intense message exchange between these two complex systems are only now becoming objects of scientific inquiry. Both neurotransmitters and cytokines affect their target cells through surface receptors and also by other molecular mechanisms. Cytokine receptors are present in neurons and glial cell populations in discrete brain regions. This review firstly focuses on the role of cytokines in hippocampal physiological processes, such as memory and learning, and secondly on the pathological involvement of cytokines in diseases like depression and epilepsy. Interleukin-1β is necessary for long-term potentiation (LTP) maintenance in the hippocampus. On the other hand, interleukin-6 has a negative regulatory role in long-term memory acquisition. Astrocyte-secreted tumor necrosis factor plays a role in synaptic strength by increasing surface translocation of glutamate AMPA receptors, and the chemokine CXCL12 can silence the tonic activity of Cajal–Retzius neurons in the hippocampus. Manifold increased concentrations of interleukin-10, interferon-γ, ICAM1, CCL2, and CCL4 are observed in the hippocampi of patients with temporal lobe epilepsy. A contemporary view of the role of cytokines as neuromodulators is emerging from studies in humans and manipulations of experimental animals. Despite the accumulating evidence of the role of cytokines on nervous system physiology and pathology, it is important not to exaggerate its relevance.

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1. Introduction

Signaling through secretion of small molecules is a hallmark of both nervous and immune systems. The scope of the intense message exchange between these two complex systems is only now becoming the object of scientific inquiry. Both neurotransmitters and cytokines affect their target cells through surface receptors and also by other molecular mechanisms. Cytokine receptors are present in neurons and glial cell populations in discrete brain regions. Cytokines are involved in a bidirectional signaling between the central nervous system and the peripheral immune system and play a role in cognitive processes [1,2]. Also, cytokines take part in the regulation of neurogenesis, the proliferation of new neurons that is crucial for hippocampal functions such as learning and memory [3,4].

Recognizing the brain as a regular organ with proliferation of all its constituent cell types has been a great advance in neurological research in the last decades. Regarding the roles that neuronal and glial proliferation and neuromodulation by cytokines play in nervous system development, expression of behaviors, and neural pathologies, the analyses of the interrelation between such phenomena will allow new venues for advances in therapeutic efforts.

This review firstly focuses on the role of cytokines in brain physiological processes, such as memory and learning, and secondly on the pathological involvement of cytokines in neuronal diseases like epilepsy. Despite the accumulating evidence of the importance of the inflammatory process in neural pathologies, it is important to maintain a balanced view. The past neglect of the relevance and even existence of phenomena such as neuroinflammation or neurogenesis should not be substituted by an exaggeration of their role on nervous system physiology and pathology.

2. Immune signaling in brain physiology

2.1. Cytokine receptors in CNS

Cytokines are small signaling molecules secreted by many cell types including the endothelium, lymphocytes, astrocytes, microglia, and

Abbreviations: CCL, C–C motif ligands (e.g., CCL2/MCP-1, monocyte chemoattractant protein-1; CCL3/MIP-1α, macrophage inflammatory protein 1 alpha; CCL4/MIP-1β, macrophage inflammatory protein 1 beta; CCL5/RANTES, regulated upon activation normal T-cell expressed); CCR, CCL receptor; CXCL, CXC motif ligands (e.g., CXCL4/PF4, platelet factor 4; CXCL12/SDF-1α, stromal cell-derived factor-1 alpha); CXCR, CXCL receptor; CX3CL1, CX3C motif ligand 1/fractalkine; HGF, hepatocyte growth factor; ICAM1, intercellular adhesion molecule 1/CD54; IFN, interferon; IL, interleukin; LTP, long-term potentiation; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule/CD106; VEGF, vascular endothelial growth factor.

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neurons. They are classified in families, and the principal ones are interleukins (IL), tumor necrosis factor (TNF), interferons (IFN), and chemokines. Chemokines are cytokines that display chemoattractant properties and have been experimentally demonstrated as neuromodulators [5]. They are denominated and classified by the number and position of cysteine residues on their N-terminal end, being grouped on four families: CC, CXC, CX3C, and XC.

Cytokines in general present a great degree of redundancy and pleiotropism, i.e., each cytokine can interact with many different cytokine receptors. Cytokine receptors are found in the hypothalamus, nucleus accumbens, hippocampus, thalamus, cortex, and cerebellum [6–10]. Like receptors for neurotransmitters, cytokine receptors present a regional distribution in the brain and are localized to specific glial and neuronal cellular populations in those regions [5,9,11]. Hippocampal pyramidal neurons, for example, possess membrane CCR2 receptors [9] and granular neurons IL-1βR1 [8,12]. Astrocytes in the adult mouse brain express, for example, the IL-9 receptor complex composed by IL-9R and IL-2Rγ [13]. The chemokine receptors CCR2, CXCR2, CXCR3, and CXCR4 are expressed by human fetal neurons [11,14].

2.2. Cytokine secretion by neurons and glia

Cytokines and chemokines are secreted by astrocytes and microglia during human fetal development, suggesting a role for chemokines on the modulation of nervous system development [15]. Cytokines are present at low concentrations in the nervous system under physiological conditions but increase manifold up to hundreds of times their basal concentrations in pathological conditions. Unstimulated adult brain human microglial cells express IL-1β, IL-6, IL-8, IL-10, IL-12, IL-15, TNF, CCL2, CCL3, and CCL4 [16]. The TNF is secreted primarily by microglia and considered to regulate microglia activation [17]. Microglia are the surveillance cells on the CNS; they are derived not from the neuroectodermal lineage but from the bone marrow (for a review, read [18]). Microglia infiltrate the nervous tissue during the early stages of embryonary development and reside throughout the brain during adult life. Its cellular pool has a high turnover rate with the recruitment of circulating monocytes to the nervous tissue where the cells differentiate into microglia [19].

Growing evidence suggests that the cytokines IL-1, IL-6, and TNF are involved in molecular and cellular mechanisms of complex cognitive processes such as learning and memory [20–22]. Multiplex immunoassay (MIA) use allows the measurement of dozens of cytokines, chemokines, and adhesion molecule protein concentration in brain extracts from both patients and experimental animals. This technological breakthrough allows the visualization of complex networks of interacting cytokines [23–25].

2.3. Cytokines in learning and memory

Learning and memory are composed of many different neural mechanisms distributed in different brain regions. Long-term potentiation (LTP) is a long-lasting increase in synaptic efficacy, which is thought to be an important underlying mechanism of learning and memory formation [26]. Episodic memory in humans and spatial navigation in rats are hippocampus-based memory and learning activities. The hippocampus is important for memory formation that is distributed in cortical areas.

Neurogenesis occurs from neural progenitor cells located in the subgranular zone of the hippocampal dentate gyrus in adult animals [27]. The newborn neurons mature into granular neurons and are synaptically integrated into the dentate gyrus [28]. The addition of new granular neurons into the dentate gyrus is necessary for hippocampus-dependent associative learning [29]. These newborn neurons were shown to play an important role in fear conditioning but not in spatial navigation learning [30]. Other studies, however, found a positive correlation between rate of neurogenesis and a spatial learning task score in aged rats [31]. Hippocampal neurogenesis is modulated by stress, for example, treatment with corticosteroids diminishes the number of neurons incorporated in the dentate gyrus [32], and is augmented by physical activity [33].

It is interesting to note that cytokines are involved in the modulation of both neurogenesis and learning in the hippocampus. The interleukin-1 (IL-1) family consists of 11 cytokines, the principal members of which are IL-1α, IL-1β, IL-1 receptor antagonist (IL-1ra), and IL-18. Interleukin-1 alpha and interleukin-1 beta display high sequence homology, and both exist as inactive forms until they are cleaved by calpain and caspase-1, respectively. Interleukin-1 beta acts as a neuromodulator in the hippocampus [34] and is necessary for long-term potentiation (LTP) maintenance [35]. Interleukin-1 beta enhances the Ca^{2+} influx through NMDA receptors by activating Src kinases that, in turn, phosphorylates NR2A/B subunits [36]. Interleukin-1 receptors are localized in the granule neurons of the hippocampal dentate gyrus [12]. As discussed further in the pathology section, deviations from the physiological levels of IL-1β, either by excessive cytokine level or by blockade of IL-1 signaling through IL-1ra, cause memory impairment [37].

Further, IL-1β regulates neurogenesis through the availability of tryptophan by inhibiting the kynurenine pathway [38] and inhibits differentiation of serotoninergic neurons in the hippocampus [39]. Administration of low doses of IL-1β 24 h prior to a learning test with the active avoidance paradigm, which consists of a lever that rats can press to prevent an imminent shock (avoidance response) or to terminate the shock after it had begun (escape response), increased the number of avoidance responses (which involves the hippocampus) but had no effect on escape responses (which are independent from the hippocampus) [40].

Interleukin-6 (IL-6) is primarily synthesized by astrocytes, and to a lesser extent, by microglia and neurons. Interleukin-6 exerts its biological effects through the formation of a hexameric receptor ligand composed of a pair of complexes formed by IL-6, the interleukin-6 receptor (IL-6R), and gp130, a converter and signal-transducing molecule [41]. The IL-6 receptor, through alternative splicing, also exists as a soluble form (sIL-6R), which, unlike most other soluble cytokine receptors, functions as an agonist. This soluble form can activate signaling responses in cells that lack the surface IL-6R but express gp130 through the direct binding of IL-6 and sIL-6R complex with gp130.

Interleukin-6 expression in the hippocampus is substantially increased during LTP both in vitro and in freely moving rats and is dependent on NMDA receptor activation [42]. Interestingly, blockade of endogenous IL-6 90 min after spatial alternation dependent on hippocampus learning resulted in a significant improvement of long-term memory, indicating a negative regulatory role for IL-6 on LTP by limiting memory acquisition [42]. In accordance with these results, mice with elevated IL-6 in the brain display impaired cognitive abilities and deficits in learning [43]. Another interleukin that plays a role in hippocampal memory formation is IL-15. It changes the expression of the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD) isoforms GAD-65 and GAD-67, decreasing interneuron GAD-67 expression in the stratum oriens of the CA1 region of the hippocampus [44]. Impairment of LTP can also be exerted by CX3CL1 in the hippocampus and seems to be mediated by adenosine receptor type 3 [45].

The TNF interacts with two high-affinity receptors that are expressed in nervous tissue: TNFR1 (p55) and TNFR2 (p75) [46]. These two receptors give TNF dual responses that can have opposite effects depending on concentration and location in the nervous system or time after lesion [47]. Inhibition of LTP by TNF through mitogen-activated protein kinase (MAPK) p38 has been demonstrated in hippocampal synapses [48]. Astrocyte-secreted TNF plays a role in synaptic strength by increasing surface translocation of glutamate AMPA receptors [49].

Hippocampal Cajal–Retzius neurons are still present in the hippocampal area CA1 stratum lacunosum-moleculare in juvenile mice (P12–P24), and they express CXCR4, the receptor for the CXCL12 chemokine [50]. An electrophysiology study revealed that CXCL12 can silence the tonic activity of Cajal–Retzius neurons. Interestingly, these cells possess few

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