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Short survey

Cytokines and cytokine networks target neurons to modulate long-term potentiation

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ABSTRACT

Cytokines play crucial roles in the communication between brain cells including neurons and glia, as well as in the brain-periphery interactions. In the brain, cytokines modulate long-term potentiation (LTP), a cellular correlate of memory. Whether cytokines regulate LTP by direct effects on neurons or by indirect mechanisms mediated by non-neuronal cells is poorly understood. Elucidating neuron-specific effects of cytokines has been challenging because most brain cells express cytokine receptors. Moreover, cytokines commonly increase the expression of multiple cytokines in their target cells, thus increasing the complexity of brain cytokine networks even after single-cytokine challenges. Here, we review evidence on both direct and indirect-mediated modulation of LTP by cytokines. We also describe novel approaches based on neuron- and synaptosome-enriched systems to identify cytokines able to directly modulate LTP, by targeting neurons and synapses. These approaches can test multiple samples in parallel, thus allowing the study of multiple cytokines simultaneously. Hence, a cytokine networks perspective coupled with neuron-specific analysis may contribute to delineation of maps of the modulation of LTP by cytokines.

1. Introduction

Brain plasticity underlies our ability to learn and modify our behavior, and can be compromised in neuropsychiatric and neurodegenerative diseases. Brain plasticity relies on synaptic plasticity, which strengthens or weakens synapses. One of the most widely used models for studying molecular mechanisms of synaptic plasticity is long-term potentiation (LTP), a cellular correlate of memory characterized by a rapid and remarkably persistent increase in synaptic transmission elicited by brief patterns of afferent activity [1]. Experimental support that LTP is causally linked to synaptic processes underlying memory continues to build [2,3]. Notably, a recent study demonstrated that fear conditioning (a type of associative memory) can be inactivated and reactivated by long-term depression (LTD) and LTP respectively [4], supporting a causal link between these synaptic processes and memory. The critical elements for establishing LTP involve membrane depolarization and NMDA receptors (NMDAR) activation [2], which allows calcium influx [5], activation of intracellular pathways (*e.g.*, calcium/calmodulin kinases, PKA, and the Rac/Pak/LIMK cascade), and morphological adaptations in spines that are essential for stable LTP [6]. LTP can be modulated by soluble messengers of the brain, such as cytokines and classic neuromodulators (*e.g.*, norepinephrine, dopamine and acetylcholine). While the role of classic neuromodulators on LTP has been extensively studied, the effects of cytokines on LTP are relatively unexplored. Importantly, a growing body of evidence indicates that cytokine networks modulate LTP under both physiological and pathological conditions [7]. In this review, we illustrate examples of direct vs indirect modulation of synaptic transmission and LTP by cytokines. We show that cytokines can directly target synapses, and present a novel approach using isolated synaptosomes which allows the study of LTP directly at the synapse. We conclude with a perspective on strategies for dissecting the identity of cytokines able to modulate LTP directly in neurons. The information provided by these novel approaches may reveal key nodes on the topology of brain cytokine-cell networks.

Cytokines constitute an extremely elaborated network of peptide signaling molecules (~5–20 kDa) that are fundamental in cell signaling. Cytokines act through receptors, and are especially important for immune cells, which synthesize and release cytokines in response to infections or tissue damage. Notably, the pattern of released cytokines depends on the nature of the antigenic stimulus, and the cell source that is being stimulated [8]. A number of factors further contribute to the high complexity of cytokine-cell networks. A prominent factor is the cytokine's

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pleiotropy nature, by which a given cytokine can induce differential, even opposite cell responses [9,10]. In addition, cytokines can cross-talk with signaling from other soluble factors; a cross-talk that is time, concentration and tissue-specific [10]. When acting on the brain, cytokines can induce fever, sleep and sickness behavior; they can also modify the mood, memory consolidation and cognition, as well as regulate neuroendocrine stress responses [8]. Indeed, a large number of cytokines can be released under multiple physiological and pathological contexts including learning, arousal, stress and neurodegeneration [7]. Brain cytokine levels are generally low at physiological-basal conditions but dramatically increase in response to infection, pathology (*e.g.*, Aβ, α-synuclein) or damage (*e.g.*, damage-associated molecular patterns, PAMP's). Based on the emerging understanding that inflammation-mediated signaling leads to cognitive deficits [11,12], it is commonly believed that neuronal functions can be impaired by high concentrations of inflammatory cytokines (*e.g.*, IL-1β, IL-6, IL-18, tumor necrosis factor-α (TNFα), interferon (IFN)-α and IFNγ), whereas anti-inflammatory cytokines (*e.g.*, IL-4, and IL-10) could have a protective role [13].

Inflammatory cytokines impair neuronal function in the adult brain by their direct effect on neurons or by indirect mechanisms mediated by non-neuronal cells (*e.g.*, microglia and astrocytes). The effects of inflammatory cytokines on brain mechanisms have been studied *in vitro* using brain slices [14,15], as well as *in vivo* by systemic treatment [16], direct infusion in the brain [17,18], and by transgenic cytokine overexpression [19,20]. In these experimental systems, elucidating neuron-specific effects of cytokines has been challenging because both neurons and non-neuronal brain cells commonly express cytokine receptors [21]. Moreover, cytokines can induce the expression and release of multiple cytokines in their target cells [20–24], thus increasing the complexity of the stimuli sensed by neurons after a challenge with a single cytokine (Fig. 1). Clarification of the brain cytokine networks and how their final effectors impact neuronal activity directly during both physiological and pathological contexts may help to identify specific therapeutic targets for inflammation-related cognitive decline.

2. Modulation of synaptic transmission by cytokine-cell networks

Cytokine networks are composed of the cytokine themselves, their receptors and their regulators. In the brain, cytokine networks are fundamental for the dynamic interaction between neurons, glia, endothelial cells, and immune cells including monocytes and lymphocytes (Fig. 1). Immune cells reach the CNS *via* blood [10] and, potentially, *via* the recently discovered meningeal lymphatic vessels [25]. At the synapse, the central element of neural connectivity, pre- and post-synaptic elements interact with processes of neighboring astrocyte and microglia *via* hormones, neurotransmitters and cytokines; these interactions have led to the concept of tri, tetra, and multipartite synapses [26]. Importantly, cytokines networks can locally modulate synaptic transmission *via* glia-neuron signaling. For instance, a recent report has demonstrated that TNFα (600 pM but not 60 pM) increases presynaptic activity as measured by the frequency of miniature postsynaptic excitatory currents (mEPSCs), in mouse hippocampal slices [27]. Using elegant genetic models, the authors demonstrated that TNFα activates TNFR1 at astrocytes, which then signal to the neurons *via* glutamate/NMDAR to increase presynaptic activity. Relevant for neuroinflammation, this TNFα-mediated modulation of astrocyte-neuron communication contributes to memory impairments in a model of multiple sclerosis (experimental autoimmune encephalomyelitis, EAE) [27]. Similar to the TNFα/TNFR1-astrocyte-glutamate/NMDAR-synapse network, neurons and glia also interact *via*

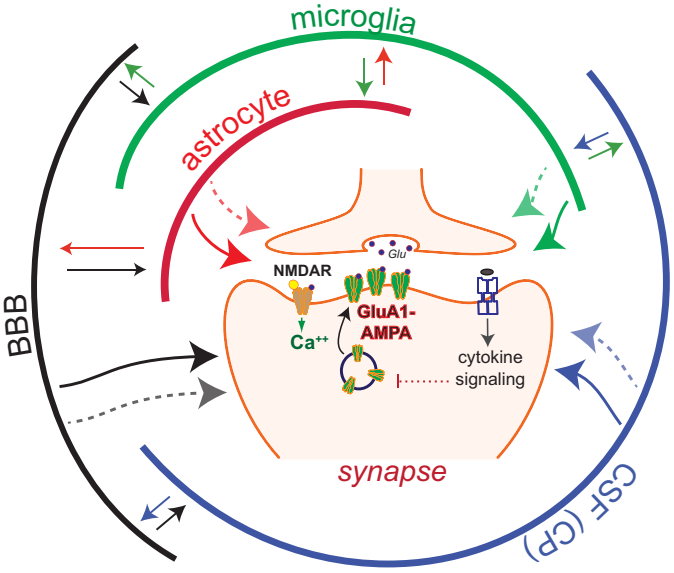

Fig. 1. Cytokines and cytokine networks modulate LTP by targeting synapses. This simplified model illustrates LTP, which relies on the NMDAR-dependent insertion of GluA1-containing AMPA receptors at the postsynaptic surface. In this model communication *via* cytokines is depicted by arrows, which can bi-directionally connect multiple cell populations. Cytokine networks enable local interactions between neuronal and non-neuronal cells (*e.g.*, astrocytes, microglia, vascular endothelial cells) in the brain, as well as brain-periphery communication *via* the brain-blood barrier (BBB) and the choroid plexus (CP). The BBB releases cytokines and regulates the flux of cytokines from the blood; the CP produces cerebrospinal fluid (CSF) and cytokines, and regulates the transport of cytokines and immune cells from blood vessels. LTP modulation by cytokines has been widely studied, however, for most cytokines, is unclear if they modulate LTP by directly targeting synapses (one-direction arrows) or by indirect mechanisms relying on cytokine networks maintained by non-neuronal cells interactions. Cytokines can induce the expression and release of multiple cytokines in their target cells, thus activating cytokine networks, which could modulate synaptic transmission by targeting synapses *via* both cytokine-dependent and −independent mechanisms (dotted arrows).