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Review

Modulation of learning and memory by cytokines: Signaling mechanisms and long term consequences

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ABSTRACT

This review describes the role of cytokines and their downstream signaling cascades on the modulation of learning and memory. Immune proteins are required for many key neural processes and dysregulation of these functions by systemic inflammation can result in impairments of memory that persist long after the resolution of inflammation. Recent research has demonstrated that manipulations of individual cytokines can modulate learning, memory, and synaptic plasticity. The many conflicting findings, however, have prevented a clear understanding of the precise role of cytokines in memory. Given the complexity of inflammatory signaling, understanding its modulatory role requires a shift in focus from single cytokines to a network of cytokine interactions and elucidation of the cytokine-dependent intracellular signaling cascades. Finally, we propose that whereas signal transduction and transcription may mediate short-term modulation of memory, long-lasting cellular and molecular mechanisms such as epigenetic modifications and altered neurogenesis may be required for the long lasting impact of inflammation on memory and cognition.

1. Introduction

Immune proteins and signaling play many key roles in the brain (Shatz, 2009). The central nervous system's own immune cells, microglia and astrocytes are required for normal synaptic functions including synaptic pruning, synapse formation and synaptic transmission (Benarroch, 2013; Papa, De Luca, Petta, Alberghina, & Cirillo, 2014; Stephan, Barres, & Stevens, 2012). A wealth of literature in animal models of inflammation supports the causal role of inflammatory signaling in memory and cognitive deficits. Systemic injection with lipopolysaccharide (LPS) impairs memory consolidation (Pugh et al., 1998), acquisition of operant conditioning (Aubert, Vega, Dantzer, & Goodall, 1995) and learning in Morris Water Maze tasks (see Cunningham & Sanderson, 2008).

In humans, systemic triggers of inflammation, including illness, injury or major surgery (Hudetz et al., 2009; Selnes et al., 2003; Shapira-Lichter et al., 2008) are associated with deficits in a variety of cognitive and memory tasks. Patients with cancer, after myocardial infarction, or major surgery commonly develop post-traumatic stress disorder (Ginzburg & Ein-Dor, 2011; Meister et al., 2013) or cognitive deficits (Fredericks, 2012) long after the illness, suggesting a persistent role for immune function in alterations of memory. Inflammatory signaling is thus considered to be a critical contributor to the short- and long term modulation of mood and cognition. However, the precise role and mechanisms by which cytokines modulate memory remain unknown.

The intricacy of inflammatory signaling presents several complications in understanding the roles and mechanisms of cytokines in neural and cognitive functions. Inflammatory events are not specific to a single cytokine increasing at a single timepoint, instead inflammation produces dynamic regulation of many cytokines (Conti et al., 2008; Gayle, Ilyin, Miele, & Plata-Salamán, 1998; Schindler et al., 1990). Cytokines are also extremely pleiotropic (e.g., Guzmán & Hallal-Calleros, 2010) and exhibit extensive redundancy, with many distinct proteins exerting overlapping effects (Liu, Fang, Guo, Mei, & Zhang, 2013). In contrast, the downstream effects of cytokines differ depending on the presence of other cytokines and specific cell types (Lund et al., 2006; Norden, Fenn, Dugan, & Godbout, 2014). Despite well-delineated interactions between cytokines within the immune system, the dynamic regulation of cytokines in the central nervous system remains unclear. Similarly, the precise roles of inflammatory signaling in the physiology of neurons, circuits, and cognitive function are not known.

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Recent work has made significant progress in establishing the effects of specific cytokines in the brain on learning, memory and plasticity. However, these studies have also uncovered contradictory roles of cytokines in modulation of memory. Given the complexity of inflammatory signaling in the brain, we propose that shifting the focus from individual cytokines to networked activation of cytokines will be a constructive way to understand the impact of inflammatory signaling on memory and cognitive function.

Here we will review the current work on individual cytokines and their effects on learning and plasticity, and begin to unpack potential mechanisms by which cytokine-dependent signaling may intersect with molecular mechanisms of memory. We will discuss both short-lasting effects via intracellular signaling cascades, as well as long lasting effects due to persistent changes in neurogenesis and epigenetic modifications.

2. Modulation of memory by cytokines

Interleukin 1β (IL-1β), Interleukin 6 (IL-6) and tumor necrosis factor α (TNFα) are among the most commonly studied cytokines in the brain (Capuron & Miller, 2011; Goehler, 2008). These proteins are strongly upregulated in the bloodstream after systemic inflammatory events such as LPS injection (Skelly, Hennessy, Dansereau, & Cunningham, 2013), sepsis model (Mina et al., 2013), surgery (Terrando et al., 2011), and other peripheral injuries (Bağdatoğlu, Polat, Bağdatoğlu, & Atik, 2008). In addition, IL-1β, IL-6 and TNFα are strongly expressed in the hippocampus after manipulations in the periphery (Burton, Sparkman, & Johnson, 2011; Cibelli et al., 2010; Datta & Opp, 2008; Ren et al., 2011) or brain (Belarbi et al., 2012) and are therefore well placed to modulate memory.

There is some evidence for involvement of IL-1β, TNFα, and IL-6 in specific memory processes including acquisition, consolidation, or retrieval. For example, peripheral IL-6 levels correlate with memory retrieval (Elderkin-Thompson, Irwin, Hellemann, & Kumar, 2012), and post-training injection of LPS disrupts consolidation of context fear conditioning via IL-1 (Pugh et al., 1998). Most studies, however, have used transgenic models, chronic injection, or acute injection of cytokine or inflammatory stimulus prior to training, demonstrating roles in modulation of learning and memory, but obscuring their role in specific memory processes.

In this section, we will describe current findings and conflicting results on the role of specific cytokines in learning and memory. Furthermore, we will describe how an interactive framework of cytokine signaling may begin to resolve difficulties in understanding the role of inflammatory signaling in the modulation of learning and memory.

2.1. Interleukin 1β

Several studies demonstrate a critical role for IL-1β in the formation of hippocampal dependent memory. IL-1β is upregulated by context fear conditioning (Goshen et al., 2007) and LTP (Balschun et al., 2003; del Rey, Balschun, Wetzel, Randolf, & Besedovsky, 2013; Schneider et al., 1998), suggesting a role for this cytokine in normal memory processing. Consistent with this, small increases (1 ng) of IL-1β injected centrally enhance context fear conditioning (Goshen et al., 2007), passive avoidance and spatial memory (C. Song, Phillips, & Leonard, 2003; Yirmiya, 2002). Adding to the evidence for the requirement of IL-1β are studies of the endogenous IL-1 receptor antagonist, IL-1ra. Overexpression of IL-1ra blocks context fear conditioning (Goshen et al., 2007), passive avoidance (Depino et al., 2004), and spatial memory (Spulber et al., 2009b; Yirmiya, 2002), as well as LTP (Goshen et al., 2007; Ross, Allan, Rothwell, & Verkhratsky, 2003). Together these findings strongly suggest that IL-1β is required for hippocampal-dependent learning and memory.

In contrast, acute intrahippocampal injection of IL-1β leads to impairments of both context fear conditioning (Gonzalez, Schiöth, Lasaga, & Scimonelli, 2009) and reconsolidation (Machado, González, Schiöth, Lasaga, & Scimonelli, 2010). Chronic overexpression of IL-1β in the hippocampus also leads to impairments of spatial memory (Moore, Wu, Shaftel, Graham, & O'Banion, 2009) and context fear conditioning (Hein et al., 2010). Similarly, application of IL-1β impairs induction and maintenance of LTP (Loscher, 2003; Ross et al., 2003; Schneider et al., 1998; Vereker, O'Donnell, & Lynch, 2000) demonstrating an IL-1β-induced deficit in hippocampal memory processes.

Adding to the complexity of the role of IL-1β, three different lines of IL-1 receptor (IL-1R) knockout mice suggest three different roles of IL-1R in memory. In IL-1R knockout mice, several studies demonstrated impaired hippocampal LTP, spatial memory, or context fear conditioning, but intact auditory fear conditioning (Avital et al., 2003; Goshen et al., 2009). In direct contradiction of this finding, other groups have shown that IL-1R knockout mice exhibit enhanced context and auditory fear conditioning (Koo & Duman, 2009). A third IL-1R knockout line failed to show any alterations in spatial or non-spatial learning tasks, or context fear conditioning (Murray, Obiang, Bannerman, & Cunningham, 2013).

These findings suggest that although IL-1β does play a role in modulating memory, the precise function strongly depends on the site of injection, timing, and dose (Goshen et al., 2007; Yirmiya, 2002). The effects are consistent with the tight negative regulation of cytokine activity by endogenous receptor antagonists (IL-1ra) (Spulber, Bartfai, & Schultzberg, 2009a) and decoy receptors (IL-1R2) (Garlanda, Dinarello, & Mantovani, 2013). Further supporting the synergistic role of interactions between IL-1β and IL-1ra is the finding that despite the impairing effects of either on their own, application of IL-1β and IL-1ra together normalizes the maintenance of LTP (Cunningham, Murray, O'Neill, Lynch, & O'Connor, 1996; Loscher, 2003; Ross et al., 2003).

Interactions between IL-1β and other IL-1 family members (Garlanda et al., 2013) likely contribute the effects on memory. For example, IL-1α is increased after passive avoidance (Depino et al., 2004). Another IL-1 family cytokine, IL-18, also regulates memory. IL-18 knockout mice (Yaguchi, Nagata, Yang, & Nishizaki, 2010), or application of IL-18 (Cumiskey, Curran, Herron, & O'Connor, 2007; Curran & O'Connor, 2001) impair memory and LTP, respectively. The ambiguity of the effects of IL-1β and IL-1R on memory, therefore is likely due to co-regulation and compensatory mechanisms of IL-1 family cytokines and their receptors (Garlanda et al., 2013).

2.2. Tumor necrosis factor α

In contrast to the bidirectional effects of IL-1β, inhibition of TNFα alone does not impair memory (Belarbi et al., 2012) and TNFα has been consistently implicated in deficits of memory and plasticity. Specifically, overexpression of TNFα in neurons or glial cells impairs passive avoidance memory (Fiore et al., 2000), synaptic plasticity (Butler, O'Connor, & Moynagh, 2004; Cunningham, Murray, O'Neill, Lynch, & O'Connor, 1996; Tancredi et al., 1992) and cerebellar learning (Paredes, Acosta, Gemma, & Bickford, 2010). Consistent with a memory impairing effect of this cytokine, TNFα mediates memory deficits after chronic LPS administration (Belarbi et al., 2012). Whereas these results suggest TNFα is not required for normal learning or memory consolidation, both TNFα and its family member TNFβ are increased after learning (Cartford, Gemma, & Bickford, 2002), and genetic deletion of both TNFα and β results in deficits across

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