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The immune system and memory consolidation: a role for the cytokine IL-1β

C. Rachal Pugh[a], Monika Fleshner[b], Linda R. Watkins[a], Steven F. Maier[a], Jerry W. Rudy[a,*]

[a]*University of Colorado at Boulder, Department of Psychology, Campus Box 345, Boulder, CO 80310, USA*
[b]*University of Colorado at Boulder, Department of Kinesiology and Applied Physiology, Campus Box 345, Boulder, CO 80310, USA*

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Abstract

Interleukin-1 beta (IL-1β), known to play a role in orchestrating the physiological and behavioral adjustments that occur during sickness, has also been shown to significantly influence memory consolidation. To support this assertion we present neurobiological evidence that the substrates for IL-1β to influence memory processing and neural plasticity exist. We then present behavioral evidence that central IL-1β administration and agents that induce central IL-1β activity impair the consolidation of memories that depend on the hippocampal formation but have no effect on the consolidation of hippocampal-independent memories. Further, we demonstrate that the impairments in hippocampal-dependent memory consolidation produced by agents that induce IL-1β activity are blocked by antagonizing the actions of IL-1β. Finally, we discuss these data in terms of their implications for a physiological role of IL-1β in memory consolidation processes and a potential role of IL-1β in producing memory impairments associated with stress, aging, Alzheimer's disease, and AIDS related dementia complex.

Keywords: Interleukin-1 beta; Memory Consolidation; Fear Conditioning; Stress; Lipopolysaccharide; gp120; AIDS Dementia; Alzheimer's Disease

1. Introduction

One of the important recent advances in understanding the biological basis of behavior is the recognition that there is extensive communication between the central nervous system and the immune system. The new field of Psychoneuroimmunology is based on the fundamental premise that there is bi-directional communication between the central nervous system and the immune system. A major contribution of this field has been the discovery that many responses to infectious agents, such as fever, increased slow wave sleep, reduced activity, exploration, and sexual behavior (that together produce a 'sickness syndrome') are orchestrated by immune products called proinflammatory cytokines that are released in response to the detection of foreign substances (antigens). Cytokines are thought to bring about these changes by their actions in the central nervous system (see Ref. [1] for a review). This idea has led to the belief that the 'sickness syndrome' does not reflect a passive organism debilitated by illness, but rather a change in the motivational state of the organism that is organized by both the central nervous system and the immune system [2].

The discovery that proinflammatory cytokines are released in the brain, however, has implications that extend beyond their role in orchestrating the "sickness syndrome". It raises the possibility that the immune system can also influence brain structures that mediate cognition [1]. The purpose of this review is to summarize a body of evidence that indicates that cytokines released in the CNS have a significant impact on cognition. Specifically, this review indicates that the proinflammatory cytokine, IL-1β, known to play a role in orchestrating the 'sickness syndrome' [1], also has a significant influence on the consolidation of memories that depend on the hippocampus.

While the focus of this paper is on the effects of IL-1β on memory consolidation, it is important to note that interleukin-1 comes in both α and β forms. IL-1α and IL-1β exist as two separate gene products that share approximately 20–30% sequence homology. They appear to exert many of the same physiological effects because both bind to the functional Type I IL-1 receptor [3]. However, IL-1β is concentrated on in the studies presented in this discussion because it is the major secreted form [4] while IL-1α remains membrane bound [5].

It is also important to point out that cytokines rarely work in isolation. Specifically, IL-1β release is normally associated with the release of the other proinflammatory

* Corresponding author. Tel.: +1-303-492-4498; fax: +1-303-492-2967.
E-mail address: jrudy@psych.colorado.edu (J.W. Rudy).

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cytokines interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) and these three cytokines have many redundant physiological effects. In fact, unpublished data from our laboratory has suggested a role for TNFα in producing some of the same memory impairments discussed in this paper. However, in order to maintain focus, the discussion in this paper is restricted to the effects of IL-1β on memory consolidation.

In addition to restricting this review to the effects of IL-1β on memory consolidation, the discussion also remains focused on the idea that IL-1β acts to impair memory consolidation in the hippocampal formation. While we believe the circumstantial evidence supporting this idea is undeniably strong, we feel that it is nonetheless important to point out that central IL-1β also affects the hypothalamus and subsequent neuroendocrine end products as well as other brain stem areas impacting most monoamine systems. While these other central effects of IL-1β may contribute to the observed memory impairments (see Refs. [6,7]) the evidence points most strongly to the involvement of the hippocampus, and thus, we once again restrict our discussion to this structure.

To support the assertion that IL-1β influences hippocampal-dependent memory consolidation, we will present neurobiological evidence that the substrates for IL-1β to influence memory processing and neural plasticity exist in the hippocampus. We will then present behavioral evidence that memories known to depend on the integrity of the hippocampus are impaired by IL-1β activity.

2. Neurobiological considerations

If IL-1β impacts memory processes mediated by the hippocampus then it should be the case that: (a) there are receptors for the protein in this structure, (b) environmental agents or events induce hippocampal IL-1β activity, and (c) IL-1β has a physiological effect on neuronal plasticity within the hippocampus. There is evidence to support all three of these criteria, suggesting that IL-1β could indeed be involved in hippocampal-dependent memory formation.

2.1. Receptor presence

Autoradiographic analysis of radiolabeled IL-1 has shown a high density of binding sites for IL-1 in the hippocampus [8]. These sites have also been confirmed by Takao et al. [9] who documented binding of radiolabeled IL-1 to hippocampal membrane preparations. Binding studies demonstrate that the highest density of IL-1β binding sites in brain are in the dentate gyrus of the hippocampus [9]. More recent studies also have confirmed the presence of IL-1 receptors in the hippocampus [10,11].

2.2. Induction of hippocampal IL-1β

It is also important to document that environmental agents or events induce IL-1β activity within the hippocampus. Several investigators [12–14] have provided strong evidence that immune system activation produces large increases in IL-1 activity in the hippocampal formation. Specifically, they report that peripheral immune activation by gram-negative bacterial cell walls (lipopolysaccharide; LPS) upregulates IL-1β mRNA in the hippocampus. However, increases in IL-1 mRNA do not necessarily mean that increased IL-1 protein will occur (see Ref. [15]). Importantly, Nguyen et al. [16] have demonstrated that immune system activation by peripheral LPS administration upregulates IL-1β protein in the hippocampal formation.

2.3. IL-1β & hippocampal plasticity

Many researchers hypothesize that neural plasticity as revealed in long-term potentiation (LTP) provides a mechanism for hippocampal-dependent memory [17,18]. If IL-1β influences hippocampal-dependent memory, then one would expect it to also influence LTP. In fact, IL-1β blocks the expression of LTP in the CA1 and CA3 regions of the hippocampus [19,20] as well as in the dentate gyrus [21,22]. This suppression of LTP is believed to be caused by IL-1 because IL-1 receptor antagonist strongly attenuates the inhibitory effect of IL-1 on LTP expression [22].

2.4. Summary

This brief review reveals that the potential for IL-1β to influence memory that depends on the hippocampus is strong. The hippocampus contains receptors for this protein, IL-1β gene expression and protein production are activated in the hippocampus by infection, and the presence of IL-1β impairs the development of synaptic plasticity.

That the hippocampus is a potential site for IL-1β effects on learning and memory is especially interesting because it is well known that damage to the hippocampus is associated with amnesia in humans (see Refs. [23,24]) and no area of the brain has been more intensely investigated in animals for its contribution to memory. Moreover, it is generally recognized that not all forms of memory depend on the hippocampus. This view is represented by a number of so-called multiple memory perspectives that distinguish between memory systems that depend on the hippocampus and memory systems that do not. Examples of such frameworks include the declarative versus nondeclarative memory systems [23,25], the locale versus taxon systems [26], the memory versus performance systems [27] and the configural versus elemental association systems [28].

The above discussion establishes the potential for IL-1β to influence memory processes mediated by the hippocampus. The key question, however, is does IL-1β impair hippocampal memory processes that influence behavior? There is now a substantial body of evidence that supports the hypothesis that IL-1β impairs hippocampal-dependent memory processes and, more specifically, that this protein exerts