

Brain Interleukin-1 Is Involved in Spatial Memory and Passive Avoidance Conditioning

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Within the brain, the inflammatory cytokine interleukin-1 (IL-1) mediates illness-associated neural, neuroendocrine, and behavioral responses; however, its role in normal neurobehavioral processes is not clear. To examine the role of IL-1 signaling in memory, we infused Long–Evans rats intracerebroventricularly with IL-1 β (10 ng/rat), IL-1 receptor antagonist (IL-1ra, 100 μ g/rat), or saline immediately following a learning task and tested memory functioning 1–8 days later. In the Morris water maze (MWM), IL-1ra caused memory impairment in the hippocampus-dependent, spatial version, whereas IL-1 β had no effect. Neither IL-1 β nor IL-1ra influenced the hippocampus-independent, nonspatial version of the MWM. In the passive avoidance response, which also depends on hippocampal functioning, IL-1ra caused memory impairment, and IL-1 β caused memory improvement. These results suggest that IL-1 signaling within the hippocampus plays a critical role in learning and memory processes. © 2002 Elsevier Science (USA)

Key Words: Interleukin-1 (IL-1); IL-1 receptor antagonist (IL-1ra); memory; Morris water maze; passive avoidance; hippocampus.

INTRODUCTION

The proinflammatory cytokine interleukin-1 (IL-1) is known to be involved in neural, neuroendocrine, and behavioral modulation during illness. Brain IL-1 is induced by many immune challenges, and via its interaction with IL-1 receptors it causes changes in several neurotransmitter systems, activation of the hypothalamus–pituitary–adrenal axis, and

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physiological changes, including fever and body-weight loss (Besedovsky & del-Rey, 1996; Yirmiya, Pollak, Morag, Reichenberg, Barak, Avitsur, Shavit, Ovadia, Weidenfeld, Morag, Newman, & Pollmacher, 2000). IL-1 within the brain also produces "sickness behavior" symptoms, including anorexia; altered sleep patterns; fatigue; and reduced locomotor, exploratory, social, and sexual behaviors (Dantzer, 2001; Yirmiya et al., 2000).

At pathophysiological levels, IL-1 (or the agents that induce it, like lipopolysaccharide, HIV glycoprotein 120, and stress) produces detrimental effects on learning and memory processes. These effects were demonstrated in the Morris water maze (MWM) (Gibertini, Newton, Friedman, & Klein, 1995; Oitzl, van Oers, Schobitz, & de-Kloet, 1993), fear conditioning (Pugh, Fleshner, Watkins, Maier, & Rudy, 2001), and autoshaping (Aubert, Vega, Dantzer, & Goodall, 1995) paradigms. The memory impairment induced by IL-1 seems to be specific to memory processes that depend on the hippocampus, whereas hippocampus-independent memories are not affected (Pugh et al., 2001). IL-1 was also shown to impair long-term potentiation (LTP), a model system for the neural mechanism underlying hippocampus-dependent memory (Bliss & Collingridge, 1993), in several hippocampal pathways (O'Connor & Coogan, 1999).

Recent evidence suggests that at least under some circumstances, IL-1 also may be required for normal memory processes: (1) The expression of IL-1, IL-1ra, and the proteins belonging to the IL-1 receptor family is particularly high in the hippocampus (Loddick, Liu, Takao, Hashimoto, & De Souza, 1998); (2) mice with targeted deletion of the IL-1 receptor type I exhibit impairments in memory and neural plasticity (Goshen, Avital, Canaan, Shohami, Iverfeldt, Richter-Levin, & Yirmiya, 2000; Goshen, Avital, Segal, Richter-Levin, & Yirmiya, 2001); (3) blocking brain IL-1 receptors by intracerebroventricular (icv) injection of IL-1ra impaired fear conditioning potentiation and learned helplessness following an inescapable shock (Maier and Watkins, 1995); (4) IL-1 β gene expression in the hippocampus is substantially increased during LTP (Schneider, Pitossi, Balschun, Wagner, Del Rey, & Besedovsky, 1998); (5) blocking IL-1 receptors with IL-1ra impaired the maintenance of LTP, without affecting its induction (Schneider et al., 1998; Coogan, O'Neil, & O'Connor, 1999); and (6) in humans, mutations in the IL-1 receptor accessory protein like gene were found to be responsible for a nonspecific form of X-linked mental retardation (Carrie, Jun, Bienvenu, Vinet, McDonell, Couvert, Zemni, Cardona, Van Buggenhout, Frints, Hamel, Moraine, Ropers, Storm, Howell, Whittaker, Ross, Kahn, Fryns Beldjord, Marynen, & Chelly, 1999; Jin, Gardner, Viswesvariah, Muntoni, & Roberts, 2000). Furthermore, the expression of this gene is particularly high in the hippocampal memory system (Carrie et al., 1999).

To further examine the hypothesis that IL-1 signaling is involved in learning and memory, rats were injected icv with either IL-1 β or IL-1ra and their performance in the MWM and passive avoidance paradigms was tested. We report here that IL-1ra caused memory impairment in the passive avoidance test and the standard version of the MWM, which assesses spatial memory. Both of these tests are associated with hippocampal functioning (Ambrogio Lorenzini, Baldi, Bucherelli, Sacchetti, & Tassoni, 1996, 1997; Morris, Garrud, Rawlins, & O'Keefe, 1982). By comparison, neither treatment affected performance in a nonspatial version of the MWM that does not depend on hippocampal mechanisms (Morris et al., 1982). In addition, IL-1 β improved memory in the passive avoidance test, while having no effect on performance in either MWM version.

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