Neurobiology of Learning and Memory **78,** 379–389 (2002)
doi:10.1006/nlme.2002.4072

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

R. Yirmiya,* G. Winocur,† and I. Goshen*

**Department of Psychology, The Hebrew University of Jerusalem, Mount Scopus, Jerusalem, 91905, Israel; †Rotman Research Institute, Baycrest Center for Geriatric Care, Toronto, Ontario, Canada; Department of Psychology, Trent University, Peterborough, Ontario, Canada; and Departments of Psychology and Psychiatry, University of Toronto, Toronto, Ontario, Canada*

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-1β (10 ng/rat), IL-1 receptor antagonist (IL-1ra, 100 μg/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-1β had no effect. Neither IL-1β 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-1β caused memory improvement. These results suggest that IL-1 signaling within the hippocampus plays a critical role in learning and memory processes.

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

The authors thank Chris Conley and Doug Caruana for excellent technical assistance in conducting the experiments. This project was partly supported by the Smith Laboratory for Collaborative Research in Psychobiology (R.Y.) and a grant from the Natural Sciences and Engineering Research Council of Canada (G.W.). R.Y. is a member of the Eric Roland Center for Neurodegenerative Diseases at the Hebrew University of Jerusalem.

Address correspondence and reprint requests to Raz Yirmiya. Fax: 972-2-5882947. E-mail: razyirmiya@huji.ac.il.

1074-7427/02 $35.00

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 lipopolysacchride, 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-1β 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, Viswesvaraiah, 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-1β 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 (Ambrogi 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-1β improved memory in the passive avoidance test, while having no effect on performance in either MWM version.

METHODS

Subjects

Subjects were male Long Evans hooded rats (6 to 8 months old) weighing between 450 and 500 g obtained from the breeding colony at Trent University. Animals were individually housed in hanging wire cages in an air-conditioned room (23 ± 1°C) with food and water ad libitum in the MWM experiment and with water deprivation before the passive avoidance experiment (see procedure below). The experiments were conducted during the light phase of a 12-h light/dark cycle, with lights on at 8 AM. The experiments were approved by the Trent University Animal Care Committee.

Stereotaxic Surgery and Intracerebroventricular Injections

Rats were anesthetized with sodium pentobarbital (60 mg/kg, ip) and placed in a stereotaxic apparatus (Model No. 900, Kopf). A burr hole was drilled 1 mm posterior to bregma and 1.5 mm lateral to the midline, and a 26-gauge stainless-steel guide cannula (Plastics-One Inc.) was lowered 4 mm below the skull surface. The tip of the guide cannula was positioned 1 mm above the lateral ventricle. The guide cannula was secured to the skull with three stainless-steel screws and dental cement and was closed by a dummy cannula (Plastics-One Inc.). For several days before the experiment, rats were handled and habituated to the icv injection procedure to minimize stress and discomfort during the experiment.

In experiments 1–3, IL-1ra (100 μg/rat, R&D Systems, Minneapolis, MN) was infused in a volume of 10 μl into the lateral ventricle. This dose was previously found to block the effects of exogenously administered IL-1 (Avitsur, Pollak, & Yirmiya, 1997a) and to impair the maintenance of LTP *in vivo* (Schneider et al., 1998). In experiments 1, 2, and 4, IL-1β (10 ng/rat) was infused in a volume of 10 μl into the lateral ventricle. We have demonstrated that this dose of IL-1 produces mild behavioral effects (e.g., anorexia) without affecting spontaneous locomotor activity (Avitsur, Pollak & Yirmiya, 1997b). Recombinant human IL-1β (with specific activity of 18,000 U/μg) was a gift from Dr. Craig W. Reynolds (Biological Response Modifiers Program, NCI, U.S.A). Infusions were made through a 33-gauge stainless-steel internal cannula (Plastics-One Inc.) which was 1 mm longer than the guide cannula. Control animals were infused with saline (same volumes). The internal cannula was connected to a microsyringe pump (Model No. 22; Harvard Apparatus) by a PE20 tube. Solutions were administered at a constant rate for 1 min. The infusion cannula was removed 1 min following the termination of the infusion to avoid spillage from the guide cannula.

The location of the icv cannulas was verified by injecting a dye (trypan blue) through each cannula at the end of the experiment. Brains were removed and cut with a scalpel, and the spread of the dye within the ventricles was examined. All cannulas were found to be in the right position.

Measurement of Learning and Memory in the MWM Paradigm

The MWM consisted of a round tank, 1.5 m in diameter, filled with water mixed with nontoxic tempera paint. Rats were given four shaping trials prior to training, in which

they were allowed a 120-s free swimming with no platform in order to get them used to swimming in the maze.

In experiment 1, spatial memory was assessed by training the rats to find the location of a hidden platform (10 cm in diameter) submerged 1.5 cm below the water surface using extra maze visual cues. The training day consisted of 12 trials. The platform remained in a permanent position in the middle of one quadrant, and the entrance point to the maze was varied randomly between trials. Rats were infused immediately after the last trial and tested 24 h later. The testing day consisted of 3 trials, following the same procedures as in training.

In experiment 2, nonspatial memory was examined by marking the platform location with a single overhead cue (a black wooden dowel 30 cm in length and 4 cm in diameter, suspended approximately 20 cm above the water surface). The location of the platform and the rat's placement in the maze alternated randomly from trial to trial. The training day consisted of 12 trials. Rats were injected immediately after the last trial and tested 24 h later. The testing day consisted of 3 trials, following the same procedure as in training.

The illumination, sound, and distal visual cues on the walls and ceiling were controlled and kept constant throughout the experiment. The latency to reach the platform was recorded manually. After each trial, the rat was placed in a holding cage, outfitted with a hot water bottle placed on a heating pad to keep it warm between trials. In each experiment, the results were analyzed by a two-way ANOVA with treatment as a between-subjects factor and day (before and after the infusion) as a within-subjects, repeated-measure factor.

Measurement of Learning and Memory in the Passive Avoidance Paradigm

Apparatus. Testing was conducted in a wood box (56 × 40 × 30 cm) with an open ceiling and a grid floor. The box was divided into start and goal areas of equal size by a manually controlled wooden sliding door. A metal spout attached to a water bottle protruded through the back wall of the goal area, 8 cm above the floor. The sliding door and water spout were connected to timers that measured latency to drink after the door was opened. In addition, the water spout and grid floor in the goal area were connected to a BRS shock generator (Model No. FGS-003) that on shock trials delivered a 1.5-mA current through the rat's mouth. This intensity may seem high, but in fact rats make very slight contact with the spout, and even with the low resistance provided by the moisture, they often experience very little of the shock. Unless the shock is high enough, passive avoidance conditioning is incomplete. Our previous experience shows that this is the minimal intensity necessary for the formation of conditioning. Illumination was provided by overhead fluorescent lighting.

Procedure. Rats were placed on a water deprivation schedule (30 min of drinking per day) for 1 week before the beginning of training. Three days of habituation followed, in which each rat was placed in the apparatus for 20 min with free access to the entire apparatus. Drinking was allowed freely during the habituation session but no other water was provided on these days. Approach training started the next day and consisted of placing the rat in the start area, sliding back the dividing door, and allowing the rat to approach the water spout and drink for 10 s. Eight such trials were administered on each day of approach training. All rats reached the criterion of approaching the spout in less

than 10 s on the last five training trials of each day. After each session rats received another 30 min of drinking in the home cage. On the following day, rats were implanted with cannulas and given 2 weeks to recover. At the beginning of the 2nd week, the water deprivation schedule was reinstated. Rats were then given 3 additional days of approach training, with the cannula attached via tubing to the infusion pump. On the 4th day, rats received three trials as before, and on the fourth trial the water spout was electrified. Thirty seconds after the shock, rats were infused in the test apparatus, with either IL-1ra or saline on experiment 3 and either IL-1 or saline on experiment 4. Rats were then returned to their home cages where water was available for 30 min. In experiment 3 one group of rats was tested 1 day post-training and -infusion and another group was tested after 8 days. In experiment 4 all rats were tested 1 and 5 days post-training and -infusion. The difference between the delays (8 vs 5 days) was dictated by practical considerations. In our experience, there is no difference in the behavior of normal rats at either delay. In the test trials of both experiments, rats were placed in the testing cage and latency to make contact with the water spout was measured. The rat was removed when contact was made or after 5 min. The results of experiments 3 and 4 were analyzed by two-way ANOVAs, with the group as a between-subjects factor and the testing day as a between- or within-subjects factor, respectively.

RESULTS

Learning and Memory in the Morris Water Maze

IL-1ra significantly impaired learning in the spatial memory paradigm, i.e., 24 h postinjection IL-1ra-injected rats displayed significantly longer latencies to reach the hidden platform than IL-1β- and saline-injected rats [$F(2, 28) = 5.832$, $p < 0.01$] (Fig. 1a). Post hoc analysis revealed a significant difference between the IL-1ra-injected group and the IL-1β injected ($p < 0.01$) or saline-injected ($p < 0.05$) groups. IL-1β caused no significant effect ($p > 0.5$) in the spatial paradigm. No difference was found between the three groups in the nonspatial paradigm ($p > 0.5$) (Fig. 1b).

Learning and Memory in the Passive Avoidance Test

IL-1ra significantly impaired long-term memory of the shock experience in the passive avoidance test [$F(1, 29) = 5.285$, $p < 0.05$] (Fig. 2). Post hoc tests revealed that on the 8th day, IL-1ra-injected rats displayed shorter latencies to touch the drinking spout compared with saline-injected rats ($p < 0.05$). IL-1β induced a time-dependent memory improvement in the passive avoidance paradigm, i.e., on the 5th, but not the 1st day postinjection; IL-1β-injected rats displayed longer latencies to touch the drinking spout compared with saline-injected rats (Fig. 3). This finding was reflected by a significant group $\times$ time interaction [$F(2, 28) = 3.408$, $p < 0.05$].

Unexpectedly, all groups in experiment 3 generally had faster running time than their counterparts in experiment 4, although training and test procedures were identical. We do not have an explanation for this finding, but it is important to emphasize that the effect was general and did not interact with experimental treatment.

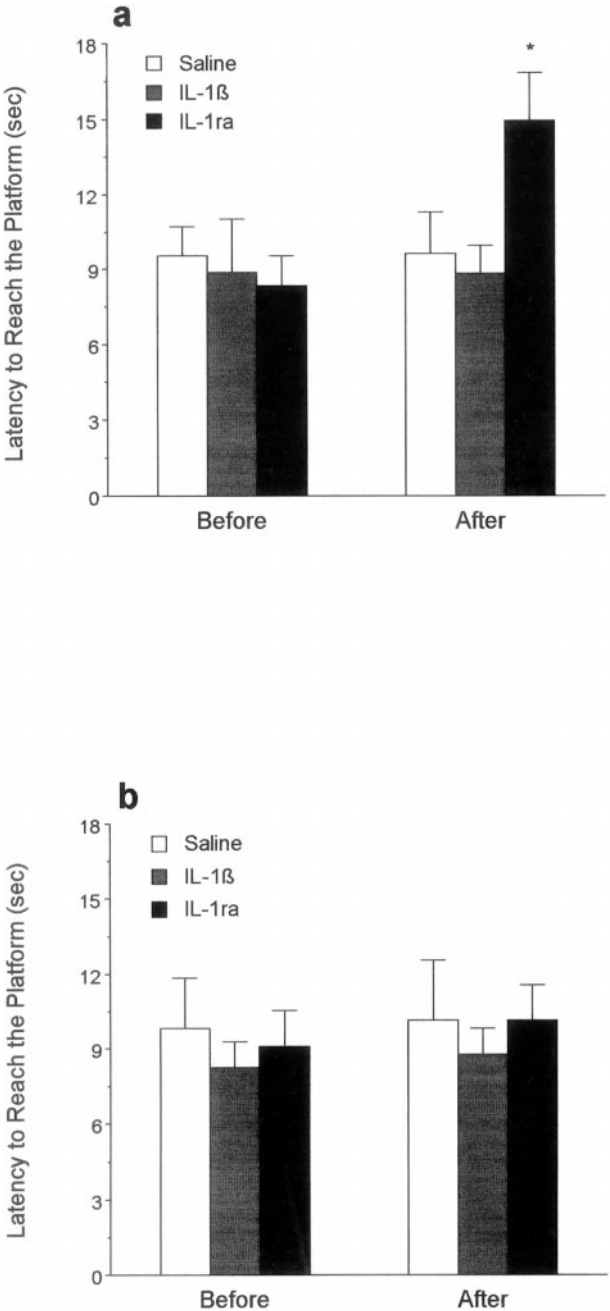

FIG. 1. Effects of icv infusion of IL-1β and IL-1ra on spatial and nonspatial memory in the Morris water maze. (**a**) In the spatial version, IL-1ra-injected rats ($n = 11$) displayed memory impairment compared to IL-1β- ($n = 12$) and saline-injected ($n = 8$) rats. (**b**) In the nonspatial version, no difference was found between the groups injected with IL-1ra ($n = 11$), IL-1β ($n = 12$), and saline ($n = 10$). Data are presented as the mean ($\pm$SEM) latency to reach the platform, on the last three trials of the training day (immediately before the injection) and the three trials of the testing day (24 h after the injection); $*p < 0.05$ compared to the IL-1β- and saline-injected groups.

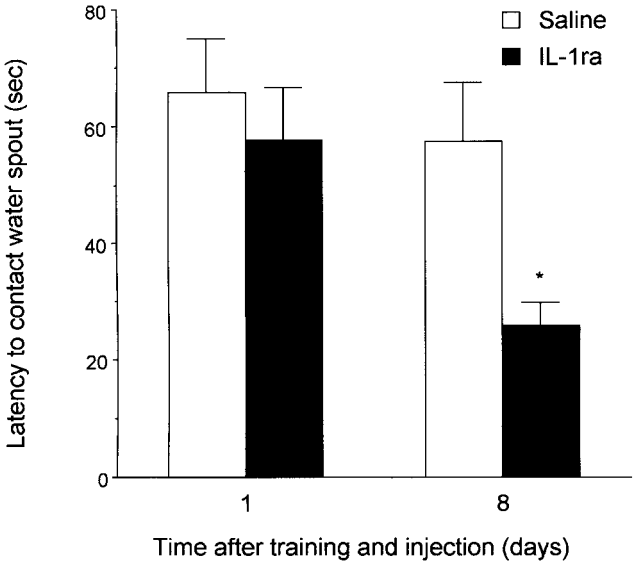

FIG. 2. Effects of icv IL-1ra infusion on passive avoidance conditioning. Rats that were injected with IL-1ra immediately following passive avoidance training and tested 1 day ($n = 9$) or 8 days ($n = 9$) postinjection, displayed memory impairment compared with the corresponding saline-injected rats ($n = 8$ and $n = 7$, respectively). Memory impairment was particularly evident 8 days postinjection. Data are presented as the mean ($\pm$SEM) to contact the water spout; $^*p < 0.05$ compared to the saline-injected group.

DISCUSSION

The results of the present study indicate that blockade of IL-1 receptors with IL-1ra produces severe memory deficits in the passive avoidance test and in the spatial, but not the nonspatial version of the MWM test. In contrast with the effects of IL-1ra, icv administration of IL-1β improved performance in the passive avoidance test, but had no effect on the spatial and the nonspatial MWM tests. Together with our previous demonstration that mice with genetic defects in IL-1 signaling exhibit profound memory disturbances (Goshen et al., 2000, 2001), these findings support the hypothesis that IL-1 signaling is involved in normal memory functioning.

Our findings with respect to IL-1β are inconsistent with previous reports that IL-1β has a detrimental effect on memory (Pugh et al., 2001; Oitzl et al., 1993; Gibertini et al., 1995; Aubert et al., 1995). In particular, Oitzl et al. (1993) demonstrated that icv infusion of IL-1β impaired spatial learning in the MWM. This discrepancy could be explained by the dose difference between the two experiments. Whereas in the previous study (Oitzl et al., 1993) a dose of 100 ng/rat was found to impair memory, we report here that a dose of 10 ng/rat had no effect. The combination of our results and the results of former studies suggests an inverted U-shape for the influence of IL-1 on spatial memory. That is, basal physiological levels of IL-1 are essential for memory, whereas higher levels can be detrimental. It should be noted however, that the same dose used in our study (10 ng/rat) caused memory impairment in the fear-conditioning paradigm (Pugh et al., 2001), suggesting that the absolute values of the inverted U-shape are different for various memory tasks. An inverted U-shaped curve has been demonstrated both for the effects of IL-1 on other processes (Ling, Potter, Lipton, & Carvey, 1998) and for the influence of other

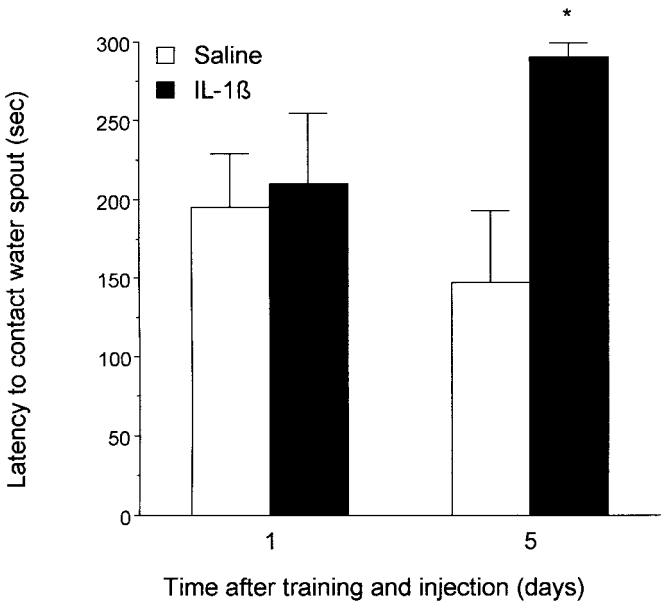

FIG. 3. Effects of icv IL-1β infusion on passive avoidance conditioning. Rats that were injected with IL-1β immediately following passive avoidance training ($n = 8$) displayed memory improvement compared to saline-injected rats ($n = 8$), at 5 but not at 1 day postinjection. Data are presented as the mean ($\pm$SEM) latency to contact the water spout; $^*p < 0.05$ compared to the saline-injected group.

substances on memory. For example, low doses of corticosterone are essential for spatial memory, whereas high doses can be detrimental (Conrad, Lupien, & McEwen, 1999).

The results of the present study suggest that IL-1 plays a role in the normal functioning of the hippocampus by demonstrating dissociation between disrupted hippocampus-dependent memory and intact hippocampus-independent memory. In the MWM, IL-1ra specifically impaired spatial, hippocampus-dependent memory, but it had no effect on nonspatial memory, which does not depend on the hippocampus (Morris et al., 1982). IL-1ra also disrupted memory in the passive avoidance test, which also requires normal hippocampal functioning (Ambrogi Lorenzini et al., 1996, 1997), whereas IL-1β improved memory in this test. These findings are consistent with previous reports that (1) the highest density of brain IL-1 receptors is within the hippocampus (Loddick et al., 1998); (2) IL-1 receptor knockout mice display disrupted short- and long-term plasticity within the hippocampus (Goshen et al., 2001); (3) IL-1 receptor knockout mice and IL-1ra transgenic mice exhibit memory deficit in hippocampus-dependent but not hippocampus-independent tasks (Goshen et al., 2000, 2001); (4) hippocampal LTP maintenance is disrupted after blockade of IL-1 receptors with IL-1ra (Schneider et al., 1998, Coogan et al., 1999); (5) IL-1 is induced in the hippocampus during LTP (Schneider et al., 1998); (6) in humans, the levels of IL-1ra are significantly correlated with endotoxin-induced impairment in declarative memory (Reichenberg, Yirmiya, Schuld, Kraus, Haack, & Pollmacher, 2001), which also depends on normal hippocampal functioning (Tulving & Markowitsch, 1998); and (7) the previously reported detrimental effects of IL-1 on memory were particularly evident in hippocampus-dependent tasks (Pugh et al., 2001; Oitzl et al., 1993; Gibertini et al., 1995). Together, these findings suggest that IL-1 exerts its influence on memory functioning within the hippocampus.

The effects of IL-1 on spatial memory may be mediated by several neural mechanisms, including IL-1-induced increase in corticosterone secretion (Besedovsky & del-Rey, 1996), p42 MAP kinase synthesis (Huwiler & Pfeilschifter, 1994), nitric oxide synthase activity (Lee, Dickson, & Brosnan, 1995), and glucose uptake (Besedovsky & del-Rey, 1996), all of which have been shown to be necessary for spatial memory (Conrad et al., 1999; Holscher, McGlinchey, Anwyl, & Rowan, 1996; Selcher, Atkins, Trzaskos, Paylor, & Sweatt, 1999; Winocur & Gagnon, 1998). IL-1 may also contribute to memory by inducing the secretion of nerve growth factor (NGF), ciliary neurotrophic factor, and other neurotrophins (Gadient, Cron, & Otten, 1990; Ishida, Yoshimura, Yoshida, Honda, Murase, & Hayashi, 1997; Kamiguchi, Yoshida, Sasaki, Inaba, Wakamoto, Otani, & Toya, 1995), which have been recently implicated in memory processes (Chen, Nishimura, Armanini, Crowley, Spencer, & Phillips, 1997; Kumon, Sakaki, Watanabe, Nakao, Ohta, Matsuda, Yoshimura, & Sakanaka, 1996; Xie, Sayan, Chen, Wei, Smith, & Liu, 2000).

Our demonstration that the effects of IL-1 on memory are not immediate (i.e., they were demonstrated after 24 h in the MWM paradigm and only after several days in the passive avoidance test) is consistent with the results of previous studies. For example, IL-1ra impaired fear conditioning enhancement and learned helplessness only when injected 24 h, but not immediately, before testing (Maier & Watkins, 1995). The beneficial effects of neurotrophins on memory (Chen et al., 1997; Kumon et al., 1996; Xie et al., 2000) may provide a possible explanation for this phenomenon because their induction by IL-1 is not immediate but takes at least 24 h to develop (Gadient et al., 1990; Ishida et al., 1997; Kamiguchi et al., 1995) and in the case of NGF may even take several days to reach its peak (Gadient et al., 1990).

In conclusion, we demonstrate here the importance of IL-1 signaling in normal hippocampus-dependent memory processes. This conclusion is consistent with the findings of several recent studies, which demonstrated the relevance of IL-1 to human memory, including the association of increased IL-1ra plasma levels with deficits in declarative memory (Reichenberg et al., 2001), the link between mutations in the IL-1 receptor accessory proteinlike gene and mental retardation (Carrie et al., 1999; Jin et al., 2000), and the connection of IL-1 gene family polymorphisms with increased prevalence and early onset of sporadic Alzheimer's disease (Grimaldi, Casadei, Ferri, Veglia, Licastro, Annoni, Biunno, De-Bellis, Sorbi, Mariani, Canal, Griffin, & Franceschi, 2000; Mrak & Griffin, 2000; Nicoll, Mrak, Graham, Stewart, Wilcock, MacGowan, Esiri, Murray, Dewar, Love, Moss, & Griffin, 2000). Thus, in humans, changes in IL-1 signaling, caused by genetic, pathological, or environmental factors, may lead to cognitive impairments.

REFERENCES

Ambrogi Lorenzini, C. G., Baldi, E., Bucherelli, C., Sacchetti, B., & Tassoni, G. (1996). Role of dorsal hippocampus in acquisition, consolidation and retrieval of rat's passive avoidance response: a tetrodotoxin functional inactivation study. *Brain Research,* **730,** 32–39.

Ambrogi Lorenzini, C. G., Baldi, E., Bucherelli, C., Sacchetti, B., & Tassoni, G. (1997). Role of ventral hippocampus in acquisition, consolidation and retrieval of rat's passive avoidance response memory trace. *Brain Research,* **768,** 242–248.

Aubert, A., Vega, C., Dantzer, R., & Goodall, G. (1995). Pyrogens specifically disrupt the acquisition of a task involving cognitive processing in the rat. *Brain, Behavior and Immunity,* **9,** 129–148.

Avitsur, R., Pollak, Y., & Yirmiya, R. (1997a). Different receptor mechanisms mediate the effects of endotoxin and Interleukin-1 on female sexual behavior. *Brain Research,* **773,** 149–161.

Avitsur, R., Pollak, Y., & Yirmiya, R. (1997b). Administration of Interleukin-1 into the hypothalamic paraventricular nucleus induces febrile and behavioral effects. *Neuroimmunomodulation,* **4,** 258–265.

Besedovsky, H. O., & del-Rey, A. (1996). Immune-neuro-endocrine interactions: Facts and hypotheses. *Endocrine Reviews,* **17,** 64–102.

Bliss, T. V. P., & Collingridge. G. L. (1993). A synaptic model of memory: Long-term potentiation in the hippocampus. *Nature,* **361,** 31–39.

Carrie, A., Jun, L., Bienvenu, T., Vinet, M., McDonell, N., Couvert, P., Zemni, R., Cardona, A., Van Buggenhout, G., Frints, S., Hamel, B., Moraine, C., Ropers, H. H., Storm, T., Howell, G. R., Whittaker, A., Ross, M. T., Kahn, A., Fryns J., Beldjord, C., Marynen, P., & Chelly, J. (1999). A new member of the IL-1 Receptor family highly expressed in hippocampus and involved in X-linked mental retardation. *Nature Genetics,* **23,** 25–31.

Chen, K. S., Nishimura, M. C., Armanini, M. P., Crowley, C., Spencer S. D., & Phillips, H. S. (1997). Disruption of a single allele of the nerve growth factor gene results in atrophy of basal forebrain cholinergic neurons and memory deficits. *The Journal of Neuroscience,* **17,** 7288–7296.

Conrad, C. D., Lupien, S. J., & McEwen, B. S. (1999). Support for a bimodal role for type II adrenal steroid receptors in spatial memory. *Neurobiology of Learning and Memory,* **72,** 39–46.

Coogan, A. N., O'Neil, L. A. J., & O'Connor, J. J. (1999). The P38 mitogen-activated protein kinase inhibitor SB203580 antagonizes the inhibitory effects of Interleukin-1b on long-term potentiation in the rat dentate gyrus in vitro. *Neuroscience,* **93,** 57–69.

Dantzer, R. (2001). Cytokine-induced sickness behavior: Where do we stand? *Brain, Behavior, and Immunity,* **15,** 7–24

Dinarello, C. A. (1996). Biologic basis for interleukin-1 in disease. *Blood,* **87,** 2095–2147.

Gadient, R. A., Cron, K. C., & Otten, U. (1990). Interleukin-1 β and tumor necrosis factor-α synergistically stimulate nerve growth factor (NGF) release from cultured rat astrocytes. *Neuroscience Letters,* **117,** 335–340.

Gibertini, M., Newton, C., Friedman, H., & Klein, T. W. (1995). Spatial learning in mice infected with legionella pneumophila or administered exogenous Interleukin-1 β. *Brain, Behavior, and Immunity,* **9,** 113–128.

Goshen, I., Avital, A., Canaan, R., Shohami, E., Iverfeldt, K., Richter-Levin, G., & Yirmiya, R. (2000). Impaired Interleukin-1 (IL-1) signaling is associated with memory impairments. *Neuroscience Letters,* **55,** S22

Goshen, I., Avital, A., Segal, M., Richter-Levin, G., & Yirmiya, R. (2001). IL-1 receptor knockout mice display impairments in hippocampal plasticity and memory functions. *Brain, Behavior, and Immunity,* **15,** 152.

Grimaldi, L. M., Casadei, V. M., Ferri, C., Veglia, F., Licastro, F., Annoni, G., Biunno, I., De-Bellis, G., Sorbi, S., Mariani, C., Canal, N., Griffin, W. S., & Franceschi, M. (2000). Association of early-onset Alzheimer's disease with an interleukin-1 alpha gene polymorphism. *Annals of Neurology,* **47,** 361–365.

Holscher, C., McGlinchey, L., Anwyl, R., & Rowan, M. J. (1996). 7-Nitro indazole, a selective neuronal nitric oxide synthase inhibitor in vivo, impairs spatial learning in the rat. *Learning and Memory,* **2,** 267–278.

Huwiler, A., & Pfeilschifter, J. (1994). Interleukin-1 stimulates de novo synthesis of mitogen-activated protein kinase in glomerular mesangial cells. *FEBS Letters,* **350,** 135–138.

Ishida, K., Yoshimura, N., Yoshida. M., Honda, Y., Murase, K., & Hayashi, K. (1997). Expression of neurotrophic factors in cultured human retinal pigment epithelial cells. *Current Eye Research,* **16,** 96–101.

Jin, H., Gardner, R. J., Viswesvaraiah, R., Muntoni, F., & Roberts, R. G. (2000). Two novel members of the interleuhin-1 receptor gene family, one deleted in Xp22.1–Xp21.3 mental retardation. *European Journal of Human Genetics,* **8,** 87–94.

Kamiguchi, H., Yoshida, K., Sasaki, H., Inaba, M., Wakamoto, H., Otani, M., & Toya, S. (1995). Release of ciliary neurotrophic factor from cultured astrocytes and its modulation by cytokines. *Neurochemical Research,* **20,** 1187–1193.

Kumon, Y., Sakaki, S., Watanabe, H., Nakao, K., Ohta, S., Matsuda, S., Yoshimura, H., & Sakanaka, M. (1996). Ciliary neurotrophic factor attenuates spatial cognition impairment, cortical infraction and thalamic degeneration in spontaneously hypertensive rats with focal cerebral ischemia. *Neuroscience Letters,* **206,** 141–144.

Lee, S. C., Dickson, D. W., & Brosnan, C. F. (1995). Interleukin-1, nitric oxide and reactive astrocytes. *Brain, Behavior, and Immunity,* **9,** 345–354.

Ling, Z. D., Potter, E. D., Lipton, J. W., & Carvey, P. M. (1998). Differentiation of mesencephalic progenitor cells into dopaminergic neurons by cytokines. *Experimental Neurology,* **149,** 411–423.

Loddick, S. A., Liu, C., Takao, T., Hashimoto, K., & De Souza, E. B. (1998). Interleukin-1 receptors: Cloning studies and role in central nervous system disorders. *Brain Research Reviews,* **26,** 306–319.

Maier, S. F., & Watkins L. R. (1995). Intracerebroventricular interleukin-1 receptor antagonist blocks the enhancement of fear conditioning and interference with escape produced by inescapable shock. *Brain Research,* **695,** 279–282.

Morris, R. G. M., Garrud, P., Rawlins, J. N. P., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature,* **297,** 681–683.

Mrak R. E., & Griffin W. S. (2000). Interleukin-1 and the immunogenetics of Alzheimer disease. *Journal of Neuropathology and Experimental Neurology,* **59,** 471–476.

Nicoll, J. A., Mrak, R. E., Graham, D. I., Stewart, J., Wilcock, G., MacGowan, S., Esiri, M. M., Murray, L. S., Dewar, D., Love, S., Moss, T., & Griffin, W. S. (2000). Association of interleukin-1 gene polymorphisms with Alzheimer's disease. *Annals of Neurology,* **47,** 365–368.

O'Connor, J. J., & Coogan, A. N. (1999). Action of the pro-inflammatory cytokine IL-1β on central synaptic transmission. *Experimental Physiology,* **84,** 601–614.

Oitzl, M. S., van Oers, H., Schobitz, B., & de Kloet, E. R. (1993). Interleukin-1β but not interleukin-6, impairs spatial navigation learning. *Brain Research,* **613,** 160–163.

Pugh, C. R., Fleshner, M., Watkins, L. R., Maier, S. F., & Rudy, J. W. (2001). The immune system and memory consolidation: A role for the cytokine IL-1β. *Neuroscience and Biobehavioral Reviews,* **25,** 29–41.

Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., & Pollmacher, T. (2001). Endotoxin-induced emotional and cognitive disturbances in healthy volunteers are associated with increased plasma levels of cytokines and cortisol. *Archives of General Psychiatry,* **58,** 445–452.

Schneider, H., Pitossi, F., Balschun, D., Wagner, A., Del Rey, A., & Besedovsky H. O. (1998). A neuromodulatory role of interleukin-1 in the hippocampus. *Proceedings of the National Academy of Sciences USA,* **95,** 7778–7783.

Selcher, J. C., Atkins, C. M., Trzaskos, J. M., Paylor, R., & Sweatt, J. D. (1999). A necessity for MAP kinase activation in mammalian spatial learning. *Learning and Memory,* **6,** 478–490.

Tulving, E., & Markowitsch, H. J. (1998). Episodic and declarative memory: Role of the hippocampus. *Hippocampus,* **8,** 198–204.

Winocur, G., & Gagnon, S. (1998). Glucose treatment attenuates spatial learning and memory deficits of age rats on tests of hippocampal function. *Neurobiology of Aging,* **19,** 233–241.

Xie, C. W., Sayan, D., Chen, Q. S., Wei, W. Z., Smith, D., & Liu, X. (2000). Deficient long-term memory and long-lasting long-term potentiation in mice with a targeted deletion of neurotrophin-4 gene. *Proceedings of the National Academy of Sciences USA,* **97,** 8816–8821.

Yirmiya, R., Pollak, Y., Morag, M., Reichenberg, A., Barak, O., Avitsur, R., Shavit, Y., Ovadia, H., Weidenfeld, J., Morag, A., Newman, M. E., & Pollmacher, T. (2000). Illness cytokines and depression. *Annals of the New York Academy of Sciences,* **917,** 478–487.