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Impaired Interleukin-1 Signaling Is Associated With Deficits in Hippocampal Memory Processes and Neural Plasticity

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ABSTRACT: The cytokine interleukin-1 (IL-1) is produced by peripheral immune cells as well as glia and neurons within the brain; it plays a major role in immune to brain communication and in modulation of neural, neuroendocrine, and behavioral systems during illness. Although previous studies demonstrated that excess levels of IL-1 impaired memory processes and neural plasticity, it has been suggested that physiological levels of IL-1 are involved in hippocampal-dependent memory and long-term potentiation (LTP). To examine this hypothesis, we studied IL-1 receptor type I knockout (IL-1rKO) mice in several paradigms of memory function and hippocampal plasticity. In the spatial version of the water maze test, IL-1rKO mice displayed significantly longer latency to reach a hidden platform, compared with wild-type controls. Furthermore, IL-1rKO exhibited diminished contextual fear conditioning. In contrast, IL-1rKO mice were similar to control animals in hippocampal-independent memory tasks; i.e., their performance in the visually guided task of the water maze and the auditory-cued fear conditioning was normal. Electrophysiologically, anesthetized IL-1rKO mice exhibited enhanced paired-pulse inhibition in response to perforant path stimulation and no LTP in the dentate gyrus. In vitro, decreased paired-pulse responses, as well as a complete absence of LTP, were observed in the CA1 region of hippocampal slices taken from IL-1rKO mice compared with WT controls. These results suggest that IL-1 contributes to the regulation of memory processes as well as short- and long-term plasticity within the hippocampus. These findings have important implications to several conditions in humans, which are associated with long-term defects in IL-1 signaling, such as mutations in the IL-1 receptor accessory protein-like gene, which are involved in a frequent form of X-linked mental retardation.
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KEY WORDS: IL-1 receptor knockout; water maze; fear conditioning; long-term potentiation (LTP); paired-pulse stimulation

INTRODUCTION

Interleukin-1 (IL-1) is a pleiotropic cytokine produced by many types of cells, including immune cells in the periphery, as well as glia and neurons within the brain (Dinarello, 1996). IL-1 signaling is mediated by a complex system, which includes the cytokines IL-1α and IL-1β, as well as IL-1 receptor antagonist (IL-1ra), which functions to block the effects of IL-1. Although many types of IL-1 receptors and receptor accessory proteins have been identified (Loddick et al., 1998), the IL-1 receptor type I appears to mediate all the known biological functions of IL-1.

In addition to its role in immunoregulation of inflammatory processes, IL-1 plays a major role in modulation of neural, neuroendocrine, and behavioral systems during illness (Rothwell and Luheshi, 2000). Thus, many immune challenges induce the production and secretion of brain IL-1, which directly produces changes in neurotransmitter and neuroendocrine systems, fever, and sickness behavior symptoms (Besedovsky and del-Rey, 1996; O'Connor and Coogan, 1999; Yirmiya et al., 2000; Dantzer, 2001). At pathophysiological levels, IL-1 can also produce detrimental effects on learning and memory processes (Oitzl et al., 1993; Gibertini et al., 1995; Aubert et al., 1995; Pugh et al., 2001). These effects appear to be specific for the consolidation of memories that depend

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on the hippocampus, whereas hippocampal-independent memories are not altered (Pugh et al., 2001). IL-1 also inhibits long-term potentiation (LTP), a model system for the neural mechanism underlying memory (Bliss and Collingridge, 1993), in several hippocampal pathways (Bellinger et al., 1993; Katsuki et al., 1990; Cunningham et al., 1996; Murray and Lynch, 1998; O'Connor and Coogan, 1999; Vereker et al., 2000).

Although most of the evidence gathered so far indicates that the effects of IL-1 on neural plasticity and memory processes are detrimental, recent evidence suggests that, at least under some circumstances, IL-1 may actually be required for the normal physiological regulation of hippocampal plasticity and learning processes: IL-1β gene expression in the hippocampus was reported to be substantially increased during LTP, both in vitro and in vivo, and blocking IL-1 receptors with IL-1ra impaired the maintenance of LTP (Schneider et al., 1998, Coogan et al., 1999b); IL-1ra also impaired memory in the water maze and passive avoidance paradigms, whereas IL-1β administration facilitated memory in the passive avoidance test (Yirmiya et al., 2002). The particularly high expression of IL-1, IL-1ra, and the proteins belonging to the IL-1 receptor family in the hippocampus (Loddick et al., 1998) may underlie the effects of IL-1 within this structure.

To examine further the hypothesis that IL-1 signaling pathways are involved in the physiological mechanisms underlying learning, memory, and neural plasticity, we used IL-1 receptor type I knockout (IL-1rKO) mice (Labow et al., 1997).

MATERIALS AND METHODS

Subjects

Subjects were male IL-1rKO mice and their 129/Sv × C57BL/6 wild-type (WT) controls (Jackson Laboratories, Bar Harbor, ME). Subjects were 2–4-month-old. Animals were housed in an air-conditioned room (23 ± 1°C), with food and water ad libitum, for several weeks before the beginning of the experiments. The behavioral experiments were conducted during the first half of the dark phase of a reversed 12-h light/dark cycle. The experiments were approved by the Hebrew University Committee on Animal Care and Use.

Measurement of Learning and Memory in the Water Maze

The water maze consisted of a round tank, 1.6 m in diameter, filled with water mixed with nontoxic gouache paint to make it opaque. In the spatial memory experiment, mice were trained to find the location of a hidden platform (16 cm in diameter), submerged 1 cm below the water surface, using extra maze visual cues. Training consisted of three trials per day, with a 1-h break between trials, for 3 days. On the fourth day of the experiment, the platform was removed and a probe trial was conducted: mice were placed in the maze for 60 s, in which the number of crosses over the former position of the platform as well as over an equal area at the center of the maze was recorded. In the nonspatial memory experiment, the platform was elevated 1 cm above the water level and therefore was visible. Mice were tested over four trials, separated by a 1-h interval. The experiments were conducted using a random protocol in which the entrance point to the maze was varied randomly between trials, and the platform remained in a permanent position. The illumination, sound, and distal visual cues on the walls and ceiling were controlled and kept constant throughout the experiment. A video camera above the pool was connected to a computerized tracking system that monitored the latency to reach the platform, the path length, and the swimming speed in each trial (VP118 tracking system, HVS Image, Hampton, UK). Mice were dried under a red light heating lamp, after each trial. The results of the learning phase were analyzed by a two-way analysis of variance (ANOVA) with the strain as a between-subjects factor and the trials as a within-subjects, repeated-measure factor. The probe test results were analyzed by Student's *t*-test.

Measurement of Learning and Memory in the Fear-Conditioning Paradigm

The fear conditioning apparatus consisted of a gray colored square conditioning cage (30 × 30 × 30 cm) with one transparent wall, to permit observation. The grid floor of the cage was wired to a shock generator and a scrambler (Coulbourn Instruments, PA). The mice were placed in the cage for 120 s. A pure tone (2.9 kHz) was then sounded for 20 s, followed by a 2-s, 0.5-mA foot-shock. This procedure was then repeated; 30 s after the delivery of the second shock, the mice were returned to their home cage; 48 h later, fear conditioning was assessed by a continuous measurement of freezing (complete immobility), the dominant behavioral fear response (Fanselow, 2000). The mice tested for contextual fear conditioning were placed in the original conditioning cage, and freezing was measured for 5 min. The mice tested for the auditory-cued fear conditioning were placed in a different context consisting of a triangular-shaped cage with no grid floor. As a control for the influence of the novel environment, freezing was measured for 2.5 min in this new cage; a 2.9-kHz tone was then sounded for 2.5 min, during which conditioned freezing was measured. Freezing was also measured during the first 120 s of the conditioning trial, before the tone and shock administration, in order to assess possible strain differences in baseline freezing. The results of the contextual- and cued-conditioning tests were analyzed by Student's *t*-test and two-way ANOVA, respectively.

Measurements of Hippocampal Activity and Plasticity In Vivo

IL-1rKO and WT mice were anesthetized with urethane (21% solution: 1.2 g/kg, i.p.) and placed in a stereotactic apparatus. A bipolar 125-μm concentric stimulating electrode was placed in the perforant path (PP) (Coordinates: 0.5 mm anterior to lambda, 2.5 mm lateral to the midline; depth, 1.95–2.05 mm). A glass pipette (diameter of 2-3 μm), containing a 2 M NaCl solution, was inserted into the dentate gyrus (DG) of the dorsal hippocampus, using an hydraulic micro-drive (coordinates: 2.0 mm posterior to bregma, 1.0 mm lateral to the midline; depth, 1.8–2.2 mm). Electrode position was opti-

mized to record maximal population spike (PS) in response to 100-μs pulse stimulation of the PP. Evoked responses were amplified, filtered at 1 Hz-1 kHz, and stored for later analysis.

After electrode insertion, recording was allowed to stabilize for 25 min. Baseline field potential responses in the DG to PP stimulation were recorded using stimulus intensity that was 50% of the intensity that evoked maximal asymptotic spike amplitude. This stimulus intensity was found to be similar in the IL-1rKO and WT control groups. Input-output relations were later examined, using three stimulus intensities (1, 2, or 3 V).

To assess short-term plasticity, paired-pulse responses were obtained thereafter. A twin pulse stimulus was delivered at three interstimulus intervals (ISIs) (15, 30, and 60 ms), and averages of five successive responses to a given stimulus intensity were quantified as the ratio of the second over the first response. Because IL-1rKO mice displayed a larger PS to the same stimulus intensity at baseline, we conducted a second experiment in which stimulus intensities given to IL-1rKO mice were adjusted to elicit baseline PS size comparable to that of controls. To assess long-term plasticity, LTP was induced by applying high-frequency stimulation (HFS) (five trains of eight 0.4-ms, 400-Hz pulses spaced 10 s apart. Stimulus intensity was 1.5 V). 10 measurements, 10 s apart were taken and averaged every 5 min, and LTP was computed as the change in the evoked responses measured during 60 min post-HFS, in comparison to pre-HFS responses. Data was collected and analyzed using Power Lab and Data Analysis software. The results were analyzed by a two-way ANOVAs, with the strain as a between subjects factor and the stimulus intensity or ISI or time after HFS as a within-subjects, repeated measure factor.

Measurements of Hippocampal Activity and Plasticity In Vitro

Hippocampal slices (350 μm) were prepared from IL-1rKO and WT mice. Experiments were performed in a submerged slice chamber, heated to 30–32°C and superfused at a rate of 2 ml/min with standard artificial cerebrospinal fluid (ACSF) containing (in mM): 124 NaCl, 2 KCl, 1.24 $KH2PO_4$, 2 $MgSO_4$, 2.5 $CaCl_2$, 26 $NaHCO_3$, and 10 glucose. pH 7.4. The ACSF was saturated with a 95%O_2/5%CO_2 gas mixture (flow rate, 0.4 L/min). A bipolar stimulating electrode (25-μm nichrome wires) was placed in the stratum radiatum of CA1 or in the molecular layer of the DG. Test stimulation of 100-μs pulse duration was delivered every 30 s, with intensity adjusted such that evoked responses were approximately 40% of maximal response. The extracellular recording electrode containing 0.75 M NaCl (2–4 MΩ) was placed in the stratum radiatum of the CA1 region for excitatory postsynaptic potential (EPSP) recording. LTP was induced by theta burst stimulation (TBS) of the Schaffer collaterals (10 trains of 4 pulses at 100 Hz separated by 200-ms ITIs at the same intensity as the test stimulation). The results were analyzed by two-way ANOVA, with the strain as a between subjects factor and the stimulus intensity or ISI or time after TBS as a within-subject, repeated measure factor.

RESULTS

Learning and Memory in the Water Maze

IL-1rKO mice displayed a slower rate of learning in the spatial memory paradigm, i.e., starting from the third trial and throughout the rest of the experiment the latencies to reach the platform were significantly longer in IL-1rKO than in their WT controls ($F(8,112) = 3.465$, $P < 0.001$) (Fig. 1a). Compared with controls, IL-1rKO mice displayed significantly slower speed of swimming (average speed = 22.37 and 16.86 cm/s, respectively; $F(1,13) = 15.371$, $P < 0.002$), suggesting that they have motor impairments. However, these impairments cannot account for the slower rate of learning, because the learning deficit was also observed with respect to the path length to reach the platform, which provides a measurement of learning that is not dependent on speed ($F(8,104) = 2.364$, $P < 0.02$) (Fig. 1b). In addition, in a 60-s probe test, IL-1rKO mice demonstrated a significantly smaller number of crosses over the former position of the platform compared with their WT controls ($t(14) = 2.414$, $P < 0.02$) (Fig. 1c). However, no difference between the two strains was found for crosses over the center of the maze ($P = 0.45$). In contrast with these findings, in the nonspatial memory paradigm (visible platform) IL-1rKO mice showed no difference from WT controls ($P > 0.5$) in either the latency to reach the platform (Fig. 1d) or the path length (data not shown).

Learning and Memory in the Fear Conditioning Paradigm

IL-1rKO mice exhibited impaired contextual fear conditioning, i.e. they displayed a significantly shorter freezing time than their WT controls ($F(1,38) = 4.73$, $P < 0.05$) in the original conditioning context, 48 h after they received a shock there (Fig. 2a). This difference cannot be attributed to an inherent diminished tendency to freeze, because IL-1rKO mice displayed normal auditory cued fear conditioning (Fig. 2b), i.e., the tone presentation had a significant effect on both groups ($F(1,23) = 123.5$, $P = 0.0001$), but there were no strain differences in either the conditioned freezing to the tone that was previously paired with foot shock ($P > 0.5$), or the baseline freezing time in the different context ($P > 0.5$).

Hippocampal Neural Responses and Plasticity In Vivo

Baseline neural activity

At each stimulus intensity, the EPSP slope was similar in both groups (Fig. 3a), whereas the PS size was enhanced significantly in the IL-1rKO mice compared with WT controls ($F(5,57) = 86.183$, $P < 0.0001$; Fig. 3b).

Paired-pulse responses

To gain insight into possible alterations in inhibitory/excitatory interactions in the DG at the local circuit level, we examined the

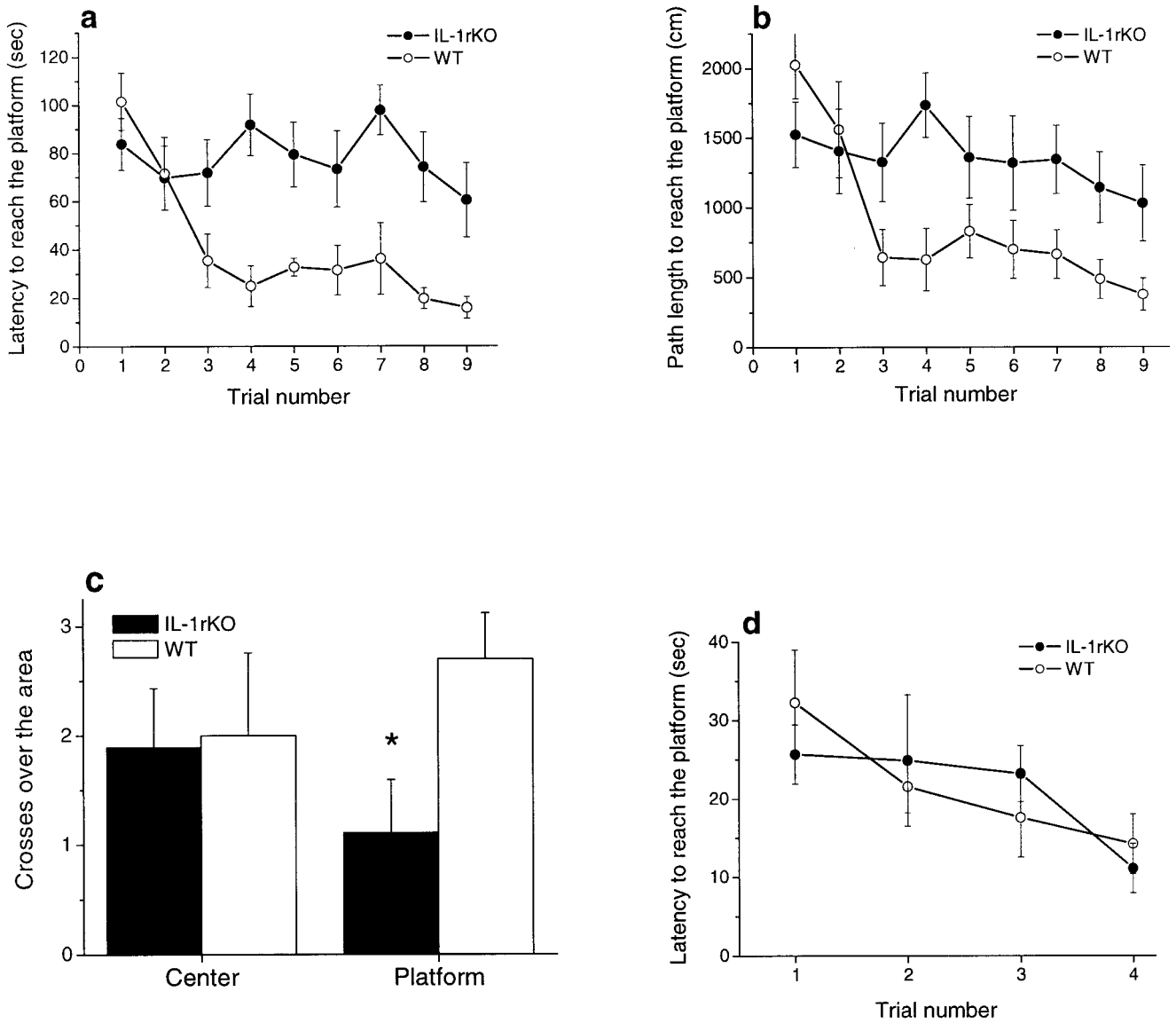

FIGURE 1. Effects of impaired interleukin-1 (IL-1) signaling on spatial and nonspatial memory in the water maze. IL-1 type I receptor-deficient mice (IL-1rKO, n = 9) displayed spatial memory impairment compared with wild-type (WT) controls (n = 7), in the latency (a) and the path length (b) to reach the platform, as well as in a probe trial performed 24 h after training (c). IL-1rKO mice (n = 6) exhibited no impairment in nonspatial memory compared with WT mice (n = 8) (d). Data are presented as the mean ±SEM.

responses to a paired-pulse stimulation applied to the PP. In control mice, the EPSP response to the second of the two stimuli was reduced to 92% at a 15-ms ISI. This suppression was reversed to facilitation at 30 and 60 ms ISIs. In contrast, in the IL-1rKO mice, the response to a second stimulus was significantly suppressed at both 15 and 30 ms ISIs. This suppression was reversed to a minor facilitation only at the longest (60 ms) ISI (Fig. 3c). These findings were reflected by a significant difference between the two groups over all ISIs ($F(5,12) = 18.54$, $P < 0.0001$).

In another experiment, we precluded a possible effect of the stimulus intensity on the observed responses, by repeating the measurements at two different intensities (1 or 2 V). Moreover, to control for the significant difference in the basal PS size between the control and the IL-1rKO mice, we adjusted the basal PS size in the IL-1rKO mice to that of the WT mice by applying lower stimulus intensities (0.8 or 1.2 V). The same pattern of results was maintained in all cases ($F(11,30) = 18.21$, $P < 0.0001$) (Fig. 3d).

Long-term potentiation

In control mice, HFS produced LTP of both EPSP slope (Fig. 3e) and PS amplitude (data not shown), which lasted for more than 60 min (EPSP = 55.88 ± 4.83%; PS = 80.42 ± 7.96%). In contrast, no LTP was produced in the IL-1rKO mice. To ensure that the absence of LTP in these mice was not due to the difference in the basal PS size, we tested another IL-1rKO group in which basal PS size was adjusted to that of the control mice (IL-1rKO-Adj). Still, no potentiation was expressed in these mice (Fig. 3e).

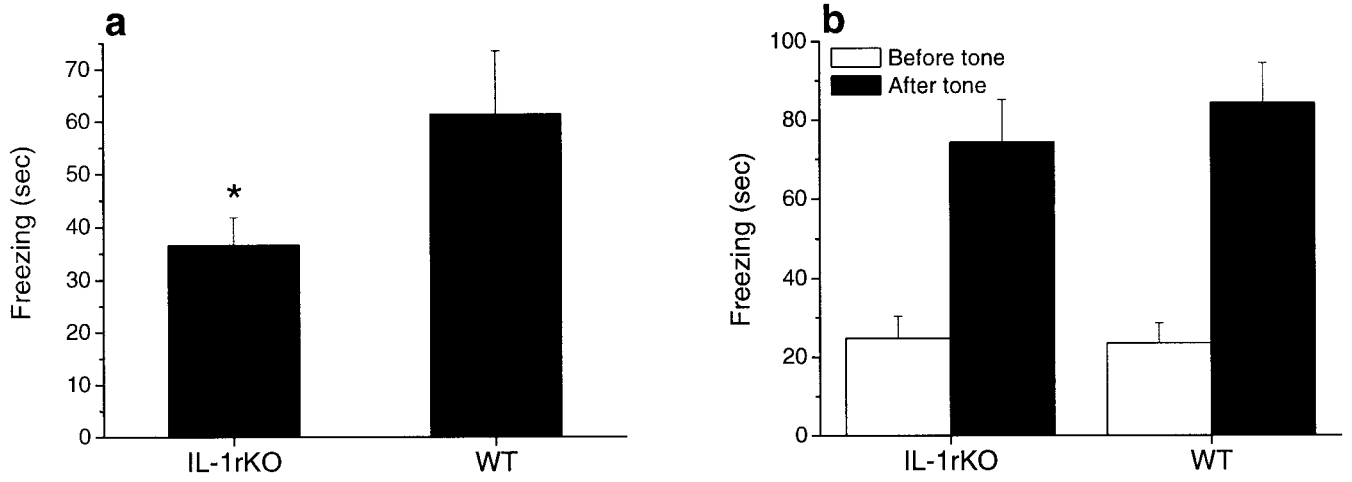

FIGURE 2. Effects of impaired interleukin-1 (IL-1) signaling on contextual and auditory-cued memory in the fear-conditioning paradigm. a: IL-1rKO (n = 21) displayed contextual memory impairment compared with wild-type (WT) controls (n = 19). (b) IL-1rKO mice (n = 13) exhibited no impairment in auditory-cued memory compared with WT mice (n = 12). Data are presented as the mean ±SEM.

Hippocampal Responses and Plasticity In Vitro

The basal properties of EPSPs in stratum radiatum of the CA1 region were examined in hippocampal slices taken from IL-1rKO and control mice. The dynamic range of the EPSPs was larger in slices taken from IL-1rKO mice than that of the control mice; consequently, the maximal EPSP was larger than that of the control mice (Fig. 4a). We then examined paired pulse paradigms at different intervals in CA1 region. Figure 4b shows representative traces of paired pulse responses measured in CA1. Unlike the finding in the DG in vivo, there was no apparent paired-pulse depression in either the control or the IL-1rKO mice in vitro. However, paired pulse facilitation in CA1 of IL-1rKO mice was significantly reduced compared with controls ($F(1,38) = 5.42$, $P < 0.05$) (Fig. 4c). We then examined the LTP of EPSPs in the CA1 region of the hippocampal slices in response to TBS of the Schaffer collaterals. Potentiation could not be produced in slices taken from IL-1rKO mice under these testing conditions (Fig. 4d).

DISCUSSION

The present study demonstrates that IL-1rKO mice display severe deficits in spatial and contextual memory, but not in nonspatial and auditory-cued memory. IL-1rKO mice also exhibited marked deficits in ability to express both short-term and long-term hippocampal plasticity in the DG in vivo and in CA1 area in vitro. These mice are shown to have no IL-1 receptor type I expression; they are reported to display no obvious developmental or immunological defects, but to have a defective response to IL-1α and IL-1β (Labow et al., 1997). Along with the impaired short-term plasticity, the behavioral findings support our hypothesis that signaling via the IL-1 receptor is critically involved in normal memory functioning and in synaptic plasticity.

In IL-1rKO mice, the baseline PS size was significantly larger than in WT controls. In addition, IL-1rKO mice exhibited greater paired-pulse inhibition in the DG and diminished paired-pulse facilitation in the CA1. These findings suggest that the lack of IL-1 signaling leads to increased baseline excitability, concomitantly with a marked expression of local circuit inhibition. IL-1rKO mice also showed a complete absence of LTP. Adjustment of baseline PS size in the IL-1rKO mice to the level seen in the control mice did not restore the ability to initiate LTP, indicating that their lack of plasticity is not due to a technical, ceiling effect. The effects of the IL-1rKO on basic synaptic properties, both in vivo and in vitro indicate that IL-1 has constitutive effects on synaptic interactions in the hippocampus, and that the lack of LTP may be only secondary to this on-going effect. The locus of effect of IL-1 on the hippocampal synapse is still unclear, and it may involve an effect on inhibitory network activity. A comparison between the results of the in vivo and the in vitro experiments yields some interesting observations. While the basic phenomenon, that of a total lack of short and long-term potentiation is replicated in the in vitro experiments, indicating that these findings are not specific to the DG but can also be seen in CA1 region, other important effects of IL-1rKO were not similar. It should be noted that in the slice experiments we measured only population EPSPs; thus, we are unable to determine whether the large difference in population spike size between the control and the IL-1rKO mice is maintained in vitro. The DG in vivo expressed a large paired pulse depression in the IL-1rKO mice, an observation that was not shared by the in vitro CA1 recording. This may be due to the presence of longitudinal inhibitory pathways in vivo, which are activated by the paired stimulation, and are not found in the slice, which does not maintain these inhibitory connections.

LTP is divided into an induction phase, which in the DG and in CA1 area depends on activation of NMDA receptors, and a late, maintenance phase, which depends on protein synthesis (Bliss and Collingridge, 1993). Application of IL-1ra was shown to have no effect on LTP induction but could suppress LTP maintenance, only when applied during this phase (Schneider et al., 1998; Coogan et al., 1999b). Because of the complete blockade of short term

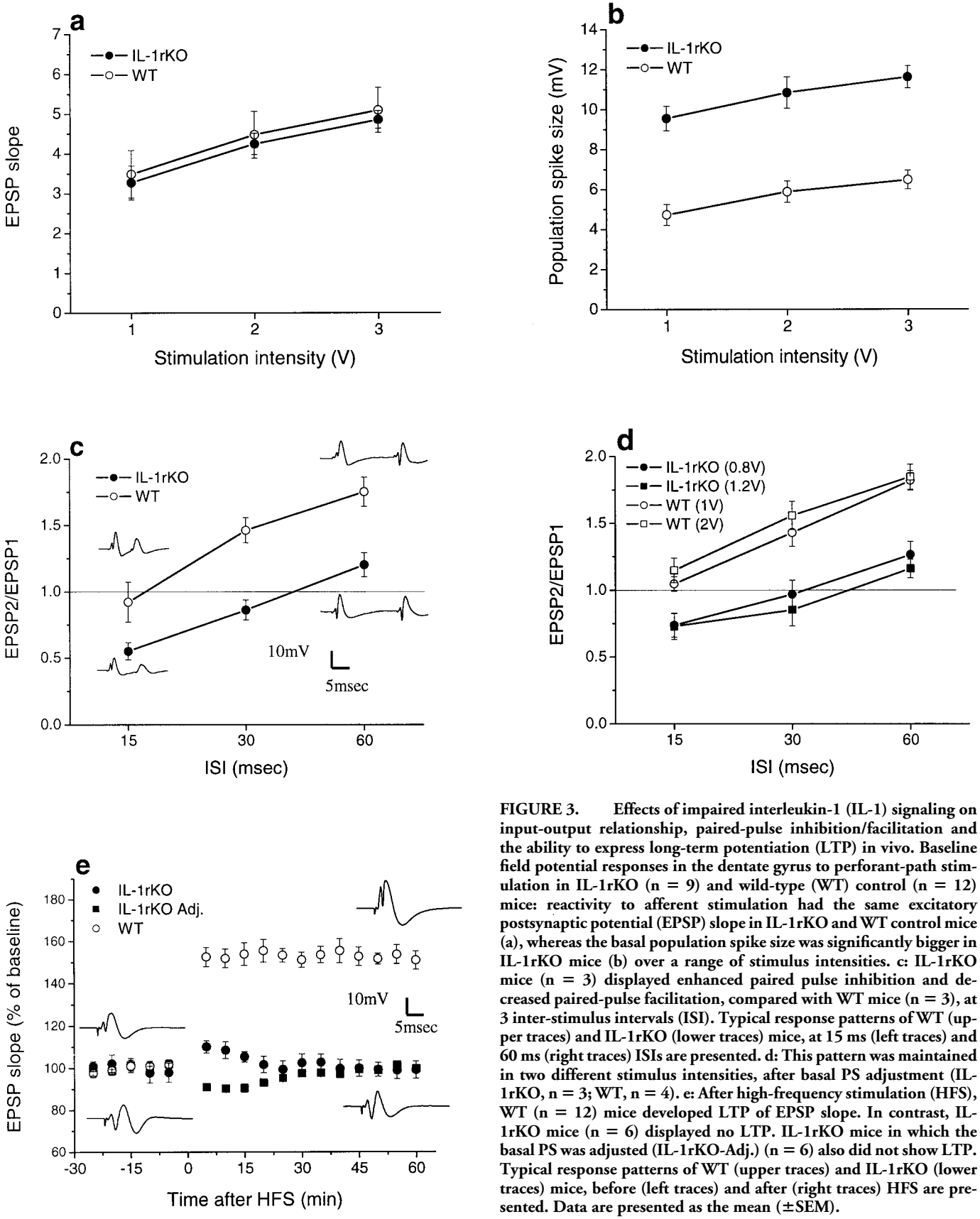

FIGURE 3. Effects of impaired interleukin-1 (IL-1) signaling on input-output relationship, paired-pulse inhibition/facilitation and the ability to express long-term potentiation (LTP) in vivo. Baseline field potential responses in the dentate gyrus to perforant-path stimulation in IL-1rKO (n = 9) and wild-type (WT) control (n = 12) mice: reactivity to afferent stimulation had the same excitatory postsynaptic potential (EPSP) slope in IL-1rKO and WT control mice (a), whereas the basal population spike size was significantly bigger in IL-1rKO mice (b) over a range of stimulus intensities. c: IL-1rKO mice (n = 3) displayed enhanced paired pulse inhibition and decreased paired-pulse facilitation, compared with WT mice (n = 3), at 3 inter-stimulus intervals (ISI). Typical response patterns of WT (upper traces) and IL-1rKO (lower traces) mice, at 15 ms (left traces) and 60 ms (right traces) ISIs are presented. d: This pattern was maintained in two different stimulus intensities, after basal PS adjustment (IL-1rKO, n = 3; WT, n = 4). e: After high-frequency stimulation (HFS), WT (n = 12) mice developed LTP of EPSP slope. In contrast, IL-1rKO mice (n = 6) displayed no LTP. IL-1rKO mice in which the basal PS was adjusted (IL-1rKO-Adj.) (n = 6) also did not show LTP. Typical response patterns of WT (upper traces) and IL-1rKO (lower traces) mice, before (left traces) and after (right traces) HFS are presented. Data are presented as the mean (±SEM).

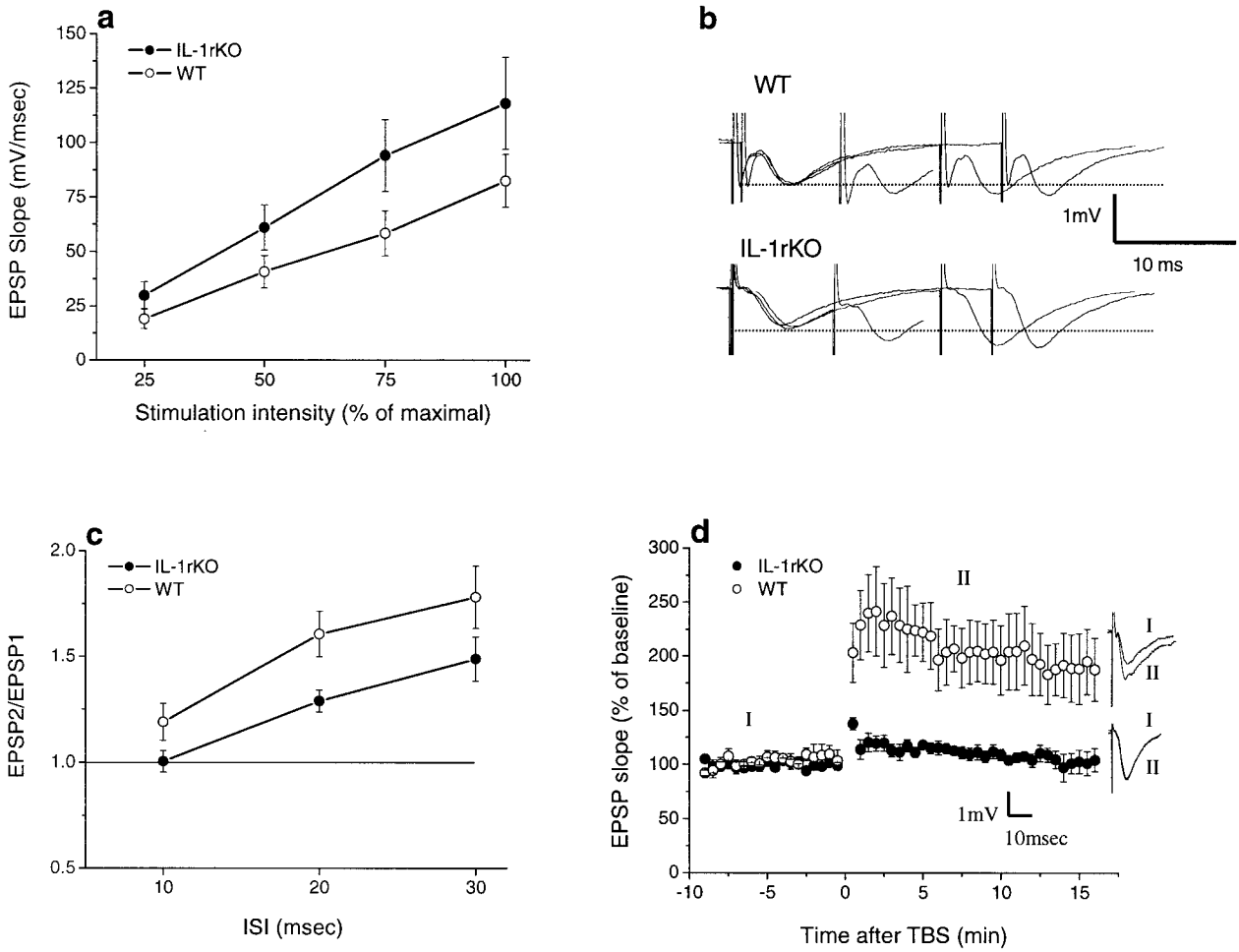

FIGURE 4. Effects of impaired interleukin-1 (IL-1) signaling on input-output relationship, paired-pulse facilitation and the ability to express long-term potentiation (LTP) in hippocampal slices. a: Input-output relationship, using four stimulus intensities, was measured in the CA1 of wild-type (WT) (n = 3) and IL-1rKO (n = 3) mice. Data represent the average (±SEM) of 8 slices. b: Sample traces of CA1 field excitatory postsynaptic potentials (EPSPs) of WT and IL-1rKO mice, showing paired pulse data pooled in c. c: Paired pulse facilitation in slices from WT (n = 3) and IL-1rKO (n = 3) mice. Recordings were made in CA1 stratum radiatum (n = 10 slices). d: LTP induced within CA1 by theta burst stimulation in WT and IL-1rKO slices (n = 8 slices taken from three mice from each strain). Representative traces of IL-1rKO (lower traces) and WT (upper traces) mice before (I) and after (II) theta burst stimulation (TBS) was given. Data are presented as the mean (±SEM). Representative traces of IL-1rKO (lower traces) and WT (upper traces) mice before (I) and after (II) TBS was given.

potentiation, it is impossible to evaluate the selective influence of IL-1 deficiency on LTP maintenance in IL-1rKO mice.

The present findings that disruption of IL-1 signaling impairs memory is consistent with our recent report that blockade of IL-1 signaling, using IL-1ra impaired memory in the water maze and passive avoidance paradigms (Yirmiya et al., 2002). However, several previous studies reported that exogenously applied IL-1β impairs LTP (Murray and Lynch, 1998; O'Connor and Coogan, 1999; Vereker et al., 2000). Moreover, most of the studies on the effects of IL-1β on learning and memory reported detrimental effects (Oitzl et al., 1993; Gibertini et al., 1995; Aubert et al., 1995; Pugh et al., 2001). The combination of our results and these other findings suggests an inverted U shape for the influence of IL-1 on memory and synaptic plasticity. Thus, basal physiological levels of IL-1 may be essential for memory and plasticity, whereas higher levels of IL-1 can be detrimental. An inverted U-shape curve has been demonstrated both for the effects of IL-1 on other processes (Ling et al., 1998) and for the influence of other substances on memory and plasticity. For example, low doses of corticosterone are essential, whereas high doses are detrimental for spatial memory and hippocampal plasticity (Diamond et al., 1992; Conrad et al., 1999).

The results of the present study indicate that IL-1 plays a role in the normal functioning of the hippocampus. The possibility that systemic knockout of IL-1 receptors may have some indirect influences on the hippocampus cannot be ruled out. However, we have preliminary results showing that mice with transgenic overexpression of IL-1ra (IL-1raTG) within the brain (under glial fibrillary acidic protein [GFAP] promoter) also display memory deficits (Goshen et al., 2002), suggesting the involvement of central, rather than peripheral IL-1 in memory processes. The behavioral results show dissociation between the disrupted spatial and contextual memory, which depends on normal hippocampal functioning, and the intact nonspatial and auditory cued memory, which do not require the hippocampus (Morris et al.,

1982; Maren, 2001). The electrophysiological findings corroborate these behavioral results by showing impairments in short-term and long-term plasticity in the hippocampus. These findings are consistent with previous reports demonstrating that (1) IL-1β mRNA levels were increased in the hippocampus during LTP (Schneider et al., 1998); (2) hippocampal LTP maintenance is disrupted after blockade of IL-1 receptors with IL-1ra (Schneider et al., 1998; Coogan et al., 1999b); (3) hippocampal-dependent memory in the water maze and passive-avoidance paradigms are impaired by IL-1ra, while hippocampal independent learning is intact (Yirmiya et al., 2002); (4) in humans, the levels of IL-1ra are significantly correlated with endotoxin-induced impairment in declarative memory (Reichenberg et al., 2001), which also depends on normal hippocampal functioning (Tulving and Markowitsch, 1998); (5) the previously reported detrimental effects of IL-1 on memory were particularly evident in hippocampal-dependent tasks (Oitzl et al., 1993; Gibertini et al., 1995; Pugh et al., 2001). Together, these findings suggest that IL-1 exerts its influence on memory functioning and neuronal plasticity within the hippocampus.

The effects of IL-1 on spatial memory and hippocampal plasticity may be mediated by various neural mechanisms, as IL-1 is known to influence the secretion of several neurotrophins, hormones, and cellular agents (Gadient et al., 1990; Huwiler and Pfeilschifter, 1994; Lee et al., 1995; Kamiguchi et al., 1995; Besedovsky and del-Rey, 1996; Ishida et al., 1997), which are involved in hippocampal memory (Kumon et al., 1996; Holscher et al., 1996; Conrad et al., 1999; Selcher et al., 1999) and plasticity (Diamond et al., 1992; Kelly et al., 1998; Coogan et al., 1999a,b; Lu et al., 1999; Xie et al., 2000). The deficits in memory and synaptic plasticity that accompany the impairment in IL-1 signaling may also result from effects of IL-1 during brain development. For example, it is possible that the lack of IL-1 during critical developmental periods leads to impairment in the formation of normal local circuit in the hippocampus, which results in abnormally enhanced feedback inhibition in these mice. IL-1 is already detectable in the embryo (De los Santos et al., 1996) and the placenta (Hu et al., 1992), and it has a direct influence on neuronal differentiation. IL-1 increases the number of progenitor cells converting into neurons and the number of extending neurons (Potter et al., 1999); it also increases the survival and induces the phenotype of dopaminergic neurons in mesencephalic progenitor cell cultures (Akaneya et al., 1995; Ling et al., 1998). Furthermore, IL-1 enhances the expression and secretion of trophic factors that influence brain development, including NGF (Gadient et al., 1990), CNTF (Kamiguchi et al., 1995), and neurotrophin-3 (Ishida et al., 1997).

The importance of IL-1 signaling in spatial memory and in short-term and long-term hippocampal plasticity is consistent with the results of several recent studies in humans, demonstrating that mutations in the IL-1 receptor accessory protein-like gene are involved in X-linked mental retardation (Carrie et al., 1999; Jin et al., 2000). In Alzheimer's disease (AD), specific IL-1 gene family polymorphisms have been shown to be associated with increased prevalence and early onset of sporadic disease (Nicoll et al., 2000). Furthermore, in the brain of AD patients the production of both IL-1 and IL-1ra is elevated, and has been shown to interact with most of the genetic and environmental risk factors for AD (e.g., progression of β-amyloid plaques, apolipoprotein E, normal aging, and head trauma) (Yasuhara et al., 1997; Mrak and Griffin, 2000). Finally, we recently demonstrated that a transient increase in plasma IL-1ra (but not IL-1) levels is associated with endotoxin-induced memory deficits in healthy volunteers (Reichenberg et al., 2001). Thus, in humans, changes in IL-1 signaling, caused by genetic, pathological, or environmental factors, may lead to cognitive impairments.

In conclusion, the results of the present study support to the notion that normal physiological levels of IL-1 have a role in some aspects of memory formation, presumably by its influence on hippocampal activity and plasticity. These results suggest that IL-1 is not only a mediator of illness-associated immune responses and neuroimmune interactions, but it may also have a critical role in normal cognitive function.

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