Interleukin-1β Abrogates Long-Term Depression of Hippocampal CA1 Synaptic Transmission

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ABSTRACT Although interleukin-1β (IL-1β) is well known to modulate synaptic transmission and plasticity of the hippocampus, no study has yet evaluated how this cytokine affects long-term depression (LTD), one of the major forms of hippocampal synaptic plasticity. Here we report that at Schaffer collateral-CA1 synapses, bath application of IL-1β induces a long-lasting decrease in synaptic strength in intact slices, but not in disinhibited slices in the presence of bicuculline, a γ-aminobutyric acid receptor antagonist. The IL-1β-induced synaptic depression efficiently foreclosed the subsequent induction of LTD in response to a 1-Hz tetanus and, conversely, it was also prevented by preexisting LTD. These results suggest that IL-1β-induced, persistent depression of synaptic efficacy is required for GABAergic activation and shares, at least in part, a common cellular mechanism for LTD. **Synapse 47:54–57, 2003.**

INTRODUCTION

Although interleukin-1β (IL-1β) was originally assigned a key role in the immune system in the periphery, accumulating evidence has also emphasized its pleiotropic functions in the brain, including host defense responses to neuroinflammation, fever, sleep, neuronal cell death, learning and memory, and neuroendocrinous modulations of synaptic transmission and plasticity (Lynch, 1998; Rothwell and Luheshi, 2000).

In the adult central nervous system, the hippocampal formation is a prominent site of expression of IL-1β (Lechan et al., 1990) and its receptor (Takao et al., 1990). In the hippocampal CA1 region, IL-1β mRNA levels steadily increase with time after the induction of long-term potentiation (LTP), a well-established cellular model of synaptic plasticity that has been proposed as a substrate for memory (Schneider et al., 1998). Exogenous IL-1β induces a sustained decrease in basal CA1 synaptic efficiency and also inhibits LTP induction in the CA1 region (Bellinger et al., 1993), the CA3 region (Katsuki et al., 1990), and the dentate gyrus (Coogan et al., 1999; Cunningham et al., 1996). More recently, IL-1β is implicated as an endogenous mediator of postischemic, age-related, and stress-induced impairment of LTP (Yamasaki et al., 1992; Murray and Lynch, 1998). Despite such observations concerning LTP, surprisingly there is no report elucidating the involvement of IL-1β in long-term depression (LTD), another major form of synaptic plasticity (Bear and Abraham, 1996). Using hippocampal slices, this work shows that brief treatment with IL-1β induces an LTD-like reduction in CA1 synaptic strength and causes no further induction of LTD in response to low-frequency stimulation and also that preceding LTD occludes IL-1β-induced synaptic depression. In addition, we report that mutant mice lacking IL-1 shows normal LTP and LTD as compared with wild-type animals.

MATERIALS AND METHODS

Hippocampal slices were prepared from male C57BL/6 mice (13–23 days old, special pathogen free, SLC, Shizuoka, Japan) or IL-1α/β knockout mice (15 days old), in

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which genes for IL-1α and IL-1β were both deleted by homologous recombination (Horai et al., 1998) and raised on C57BL/6 background, in accordance with the Japanese Pharmacological Society guide for the care and use of laboratory animals. After decapitation, the brain was removed and cut into four to six slices (400 μm each) in ice-cold media containing (in mM): 127.0 NaCl, 1.6 KCl, 1.24 KH_2PO_4, 2.4 $CaCl_2$, 1.3 $MgSO_4$, 26.0 $NaHCO_3$, and 10D-glucose (Ueno et al., 2002). The slices were equilibrated on nets positioned over wells at the interface of humidified O_2 (95%) and CO_2 (5%) maintained at 32°C for at least 1 h before physiological recordings. Bipolar stimulating electrodes (150-μm pole separation) were positioned about 350 μm apart on a single extracellular recording electrode (glass micropipette filled with 0.12 M NaCl) put in the middle of CA1 stratum radiatum. Test stimuli (50-μsec duration) were delivered at one per 30 sec. The half-maximal responses of the initial slopes of field excitatory postsynaptic potentials (fEPSPs) were monitored for at least 30 min before drug application or the induction of LTD. Agents were delivered by perfusion of the media containing the desired concentration of drugs.

Human recombinant IL-1β was obtained from Boehringer Mannheim Biochemica (Mannheim, Germany) with >98% purity (the endotoxin level was less than 10 EU/ml). Bovine serum albumin (1 μg/ml) was used as a carrier protein to prevent the loss of IL-1β by nonspecific binding of IL-1β to the tubing, slice chamber, etc. The albumin alone did not affect synaptic transmission, LTP, or LTD magnitude (data not shown).

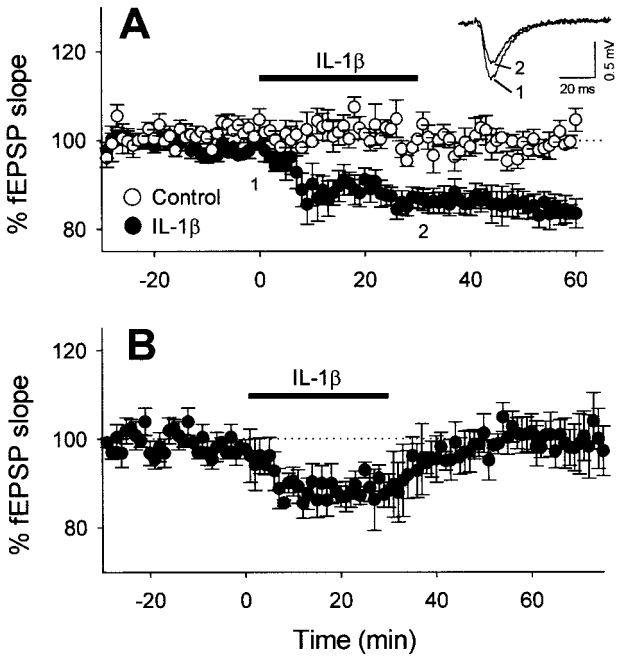

Fig. 1. Requirement of GABAergic activity for IL-1β-induced long-lasting depression. **A:** Bath application of 1 ng/ml IL-1β for 30 min produced a sustained decrease in basal CA1 synaptic transmission evoked by stimulation of Schaffer collateral/commissural fibers. Representative fEPSP recordings at time −1 and 30 are shown in the inset. **B:** Disinhibited slices in the presence of 3 μM bicuculline were treated with 10 ng/ml IL-1β for 30 min. IL-1β induced no persistent depression in disinhibited slices. The ordinate is expressed as a percentage of the average values of control slices at corresponding times after normalization. Data represent means ± SEM of 12–13 slices.

RESULTS

In our experimental conditions, basal CA1 synaptic transmission evoked by stimulation of Schaffer collateral/commissural fibers was substantially stable for the duration of the experiment (>3 h, data not shown). After bath application of 1 ng/ml IL-1β, however, fEPSP slopes gradually decreased and reached an apparent steady state after 10 min (Fig. 1A). This depression persisted for >1 h even after IL-1β washout. The average percentage of fEPSP slopes 40 min after washout to baseline level was 97.9 ± 4.3% in untreated slices and 77.8 ± 2.8% in IL-1β-treated slices (means ± SEM of 4 and 13 slices, respectively, $P < 0.01$, Student's *t*-test). IL-1β at a concentration as high as 10 ng/ml produced a similar degree of depression (75.6 ± 5.4%, $n = 12$), which suggests that an ~25% decrease is a saturation level of the IL-1β effect.

IL-1β is reported to enhance inhibitory responses to γ-aminobutyric acid (GABA) in cultured cortical neurons (Miller et al., 1991) and to hyperpolarize the membrane of amygdala neurons through enhancement of GABAergic function (Yu and Shinnick-Gallagher, 1994). To determine whether IL-1β-induced, persistent depression of fEPSPs is meditated by an alteration of GABAergic activity, IL-1β was applied to slices pharmacologically disinhibited by continuous perfusion with 3 μM bicuculline, a $GABA_A$ receptor antagonist. In these slices, application of IL-1β induced a similar decrease in fEPSPs, but within 20 min of washout fEPSP returned to control levels and no prolonged depression was observed (Fig. 1B).

When a high-frequency tetanus (100 Hz for 1 sec) was delivered to intact slices, fEPSP was immediately increased, resulting in robust LTP (152.1 ± 7.3% after 60 min, $n = 4$). However, the slices pretreated with 1 ng/ml IL-1β for 10 min displayed no significant potentiation (108.3 ± 8.9% to pretetanus levels, $n = 5$). These results confirm a previous report showing that exogenously applied IL-1β inhibits LTP induction at CA1 synapses (Bellinger et al., 1993). However, no study has yet evaluated the effect of IL-1β on the induction of LTD.

Homosynaptic LTD was readily induced by low-frequency stimulation (1 Hz for 15 min) in intact slices (Fig. 2). In the slices that had undergone synaptic depression by pretreatment with 10 ng/ml IL-1β, the same repetitive stimulation induced no further decrease in fEPSPs (Fig. 2A). Likewise, the slices that had received low-frequency stimulation displayed no additional depression by posttreatment with 10 ng/ml IL-1β (Fig. 2B). Taken together, IL-1β-induced depression prevented LTD and vice versa.

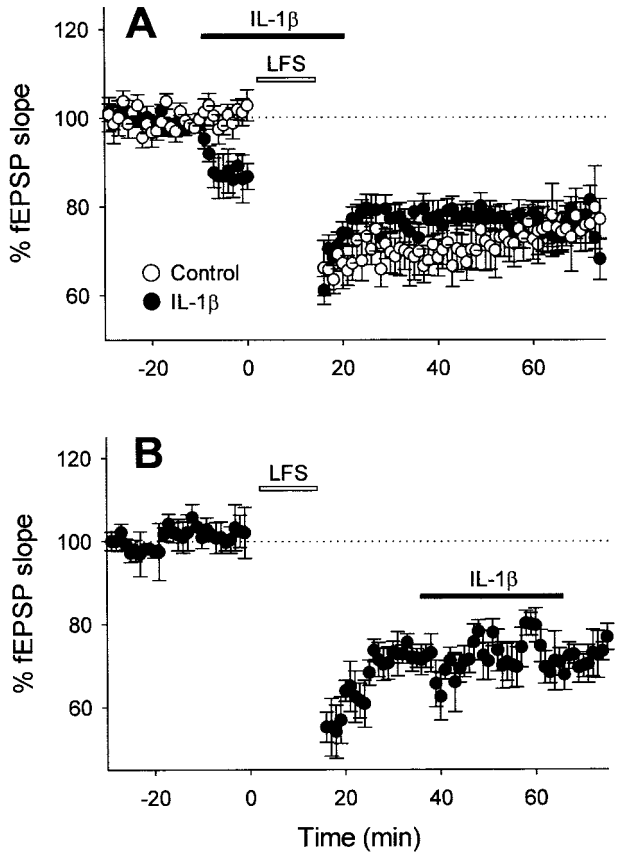

Fig. 2. Mutual occlusion of IL-1β-induced long-lasting depression and LTD in hippocampal slices. **A:** Low-frequency stimulation (LFS, 1 Hz for 15 min) was delivered to slices 10 min after application of 10 ng/ml IL-1β. IL-1β was washed out 5 min after the tetanus. **B:** IL-1β was perfused from 20–50 min after LFS. IL-1β-induced long-lasting depression prevents LTD and vice versa. Data are means ± SEM of each 9–13 slices.

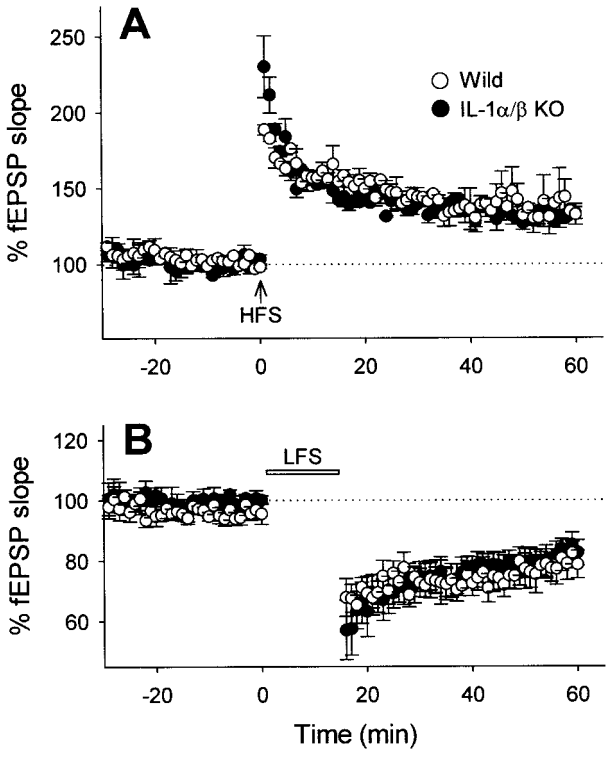

Fig. 3. Normal LTP and LTD in IL-1α/β double-knockout mice. Slices were tetanized at 100 Hz for 1 sec **(A:** high-frequency stimulation, HFS) or at 1 Hz for 15 min **(B:** low-frequency stimulation, LFS). There was no difference in LTP or LTD magnitude between wild and mutant mice. Data represent means ± SEM of 10 slices.

To determine whether or not endogenous IL-1 contributes to synaptic plasticity, we finally evaluated LTP and LTD in mutant mice lacking IL-1α and IL-1β genes. High-frequency (100 Hz for 1 sec) or low-frequency stimulation (1 Hz for 15 min) was delivered to each 10 slices prepared from IL-1α/β double-knockout mice or age-matched, wild-type littermates. We found no evidence that either LTP or LTD was altered in the absence of endogenous IL-1α and IL-1β (Fig. 3).

DISCUSSION

Although the IL-1β modulation of hippocampal synaptic transmission and plasticity has attracted much attention in various physiological and pathological aspects, e.g., infection, aging, stress, and neurodegeneration, it remains unclear how IL-1β alters frequency-dependent plastic changes in synaptic strength. We have shown for the first time that IL-1β induces a persistent synaptic depression in a GABAergic activity-dependent manner and that the IL-1β effect and homosynaptic LTD are mutually exclusive.

It is intriguing to find that in the presence of a $GABA_A$ receptor antagonist, IL-1β induces only a transient (but not persistent) inhibition of synaptic efficacy. This suggests that IL-1β-induced synaptic depression involves two distinct mechanisms, i.e., a GABA receptor-independent, acute phase and a GABA receptor-dependent, maintenance phase. A recent study shows that KCl-stimulated glutamate release is reduced in synaptosomes prepared from IL-1β-treated hippocampus (Vereker et al., 2000). Thus, the GABA receptor-independent action of IL-1β may be mediated by a direct action to excitatory presynaptic sites, while the other effect of IL-1β is possibly mediated by indirect stimulation of GABAergic interneurons. In other brain regions, several reports showed that IL-1β enhances GABA receptor function (Miller et al., 1991; Yu and Shinnick-Gallagher, 1994). A similar GABAergic potentiation may underlie the induction of long-lasting depression at CA1 synapses. Interestingly, the acute and persistent effects of IL-1β were both abrogated by prior LTD. CA1 LTD is generally believed to depend on postsynaptic activation of *N*-methyl-D-aspartate receptors (Bear and Abraham, 1996). Therefore, IL-1β and low-frequency stimulation may initially activate independent signaling pathways but at some later step converge on a common molecular event.

The present study has shown that IL-1β inhibits both LTP and LTD, suggesting that neurons exposed to IL-1β are deprived of the capability of synaptic plasticity. On the other hand, the result of intact LTP and LTD in IL-1α/β double-knockout mice demonstrates that endogenous IL-1β does not contribute to hippocampal synaptic plasticity, at least under basal conditions. Then what is the functional significance of the IL-1β modulation of synaptic plasticity? The concentration used for exogenous application may be closer to the high levels of IL-1β observed in vivo during pathological conditions such as infection, rather than the exceedingly low levels of IL-1β present in the brain under normal circumstances (Jankowsky and Patterson, 1999). Our results with IL-1β, therefore, suggest a possible link between the immune system and hippocampal-dependent memory. Another line of evidence shows that IL-1β levels in the CA1 region are increased after LTP induction (Schneider et al., 1998). Elevated expression is evident 1 h after tetanus and reaches levels nearly 16-fold higher than control within 2–3 h. Considering our findings, such considerable IL-1β upregulation probably causes an inhibition of succeeding LTP and LTD. We thus consider that IL-1β serves as a temporal factor rendering a time window for synaptic plasticity, which may play a role in excluding excessive and redundant synaptic plasticity that causes pathological deterioration of neuronal function. To address this possibility, further investigation is now under way by analyzing IL-1α/β double-knockout mice.

In conclusion, we have shown that a brief application of IL-1β inhibits basal synaptic transmission, LTP, and LTD at hippocampal CA1 synapses. Thus, IL-1β seems to rapidly calm down both neuronal activity and plasticity of the entire neural network. Such prompt, broad suppressions may represent a unique mechanism to provide a dynamic modification (and also probably a pathological aberration) of brain functions.

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