Pergamon

www.elsevier.com/locate/neuroscience

PII: S0306-4522(00)00498-X

Neuroscience Vol. 102, No. 2, pp. 273–280, 2001

0306-4522/01 $20.00+0.00

THE EFFECTS OF THE BACTERIAL ENDOTOXIN LIPOPOLYSACCHARIDE ON SYNAPTIC TRANSMISSION AND PLASTICITY IN THE CA1-SUBICULUM PATHWAY *IN VIVO*

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Abstract—Lipopolysaccharide is derived from the cell wall of gram-negative bacteria and is a potent endotoxin which causes the release of cytokines in the CNS. We examined the effect of lipopolysaccharide on synaptic transmission and synaptic plasticity in the hippocampal area CA1-subicular pathway *in vivo*. We found that lipopolysaccharide did not affect baseline synaptic transmission in this pathway; it did, however, reduce the magnitude of paired-pulse facilitation, a form of short-term plasticity thought to be primarily presynaptic in origin. We then examined the interaction between lipopolysaccharide and two common models for the biological basis of memory: high-frequency stimulation induced long-term potentiation and low-frequency stimulation induced long-term depression of synaptic transmission. We found that lipopolysaccharide blocked long-term potentiation following high-frequency stimulation and also induced potentiation of synaptic transmission after low-frequency stimulation. Lipolysaccharide blocked paired-pulse facilitation selectively at short rather than longer interstimulus intervals. Thus, lipopolysaccharide has different effects on synaptic transmission in this pathway depending on the frequency and length of stimulation.

These results provide new insights into the action of lipopolysaccharide on various forms of plasticity in the hippocampus, an area known to play a vital role in learning and memory. © 2001 IBRO. Published by Elsevier Science Ltd.

Key words: lipopolysaccharide, synaptic plasticity, subiculum, cytokines, hippocampus, synaptic transmission.

Information regarding the brain structures associated with the responses after stimulation of the endocrine and immune systems is scarce. One brain area which plays a vital role in the coordination of responses to stress and harmful threats is the hippocampal formation.[16] Stress is known to trigger the release of glucocorticoids, which are necessary for survival,[18] but elevated and prolonged corticosterone levels have been implicated in hippocampal degeneration resulting in spatial learning and memory deficits.[15] Certain cytokines, especially the pro-inflammatory ones, for example IL-1 and tumour necrosis factor (TNF), are synthesised and released during pathological events[11] and also in response to infection or injury.[24,10,27] The cytokine IL-1 alters a variety of activities characteristic of the brain–endocrine–immune response to stress.[27] Receptors for IL-1 have been located in the brain, with the highest density in the hippocampus.[3,10]

The exact role which cytokines play in synaptic plasticity is unclear. It has been shown that IL-1 beta inhibits the induction of long-term potentiation (LTP; a popular model for some of the biological processes that may be engaged during the consolidation of memories) in area CA1 of the rat hippocampus[4,10] and hippocampal area CA3 in the mouse brain *in vitro*.[14] Lipopolysaccharide (LPS) is derived from the cell wall of gram-negative bacteria and is a potent endotoxin which causes the release of cytokines such as IL-1 and TNF.[12] Recently this endotoxin has also been shown to inhibit LTP in the rat dentate gyrus *in vitro*.[10] Stressors produce many of the same neural and endocrine responses as those that follow LPS challenge.[22] Therefore, LPS activates both the immune and stress response system[13] but its exact role in relation to synaptic plasticity remains unknown.

The subiculum is the major output structure of the hippocampus[1] and is vital for learning and memory.[21] The subiculum projects to multiple cortical and subcortical targets, including the hypothalamus;[29] this latter projection may allow the subiculum to contribute to the stress response system via the hypothalamic–pituitary–adrenal axis. At present there are few data regarding the effects of LPS on synaptic transmission. We have previously shown that the hippocampal area CA1-subiculum projection can sustain a wide variety of plastic changes in synaptic transmission[5–7] and in particular that synaptic transmission in this projection is sensitive to behavioural stress. In this paper we examine firstly whether LPS has an effect on baseline synaptic transmission. We further investigate the interaction between LPS and paired-pulse

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Abbreviations: AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-propionate; EPSP, excitatory postsynaptic potential; fEPSPs, field excitatory post-synaptic potentials; HFS, high-frequency stimulation; ISI, interstimulus intervals; LFS, low-frequency stimulation; LPS, Lipopolysaccharide; LTP, long-term potentiation; PPF, paired-pulse facilitation; TNF, tumour necrosis factor.

facilitation (PPF, considered to be a short-term plastic effect).[33] We investigate whether LPS inhibits LTP in this projection in common with other areas of the hippocampus.[10] Finally, we examine the interaction between LPS and low-frequency stimulation (LFS; a protocol commonly used to produce long-lasting decreases in synaptic efficacy). These experiments may provide insight into the effects of LPS on various types of synaptic plasticity.

EXPERIMENTAL PROCEDURES

Adult male Wistar rats (BioResources Unit, University of Dublin; weight: 200–300 g) were used. Rats were housed in pairs in a temperature-controlled laminar airflow cupboard, and maintained on a 12-h light/dark cycle (08:00–20:00). All testing was carried out during the light phase. Rats were taken out of their home cages and injected i.p. 4 h prior to anaesthesia with either LPS (100 μg/kg obtained from *Escherichia Coli*; (L-2630 100 mg; Sigma Chemical, St Louis, MO, USA) or saline (0.9%). Rats were initially anaesthetised with sagatal (sodium pentobarbitone: 60 mg/kg, i.p.) and were mounted in a stereotactic holder. Further injections of urethane (ethyl carbamate: 1.5 g/kg, i.p.) were given to sustain anaesthesia throughout the experiments. A local anaesthetic/adrenaline combination was injected under the scalp and an incision was made to visualise the skull. Stimulating electrodes were aimed at area CA1 and the recording electrodes at the dorsal subiculum. Electrode implantation sites were identified using stereotaxic coordinates, relative to bregma;[23] recording and stimulating electrodes were 6.8 mm posterior and 4.0 mm lateral to the midline and 4.5 mm posterior and 2.5 mm lateral to the midline, respectively. Bipolar stimulating and monopolar recording electrodes consisted of two pieces of twisted 50-μm tungsten wire, insulated to the tips.

Signals were filtered between 0.1 Hz and 1 Khz and then amplified (DAM-50 differential amplifier, World Precision Instruments, Hertfordshire, UK). Recordings were digitised online using a PC connected to a CED-1401 plus interface (CED, Cambridge, UK). Signals were also monitored using an oscilloscope. Electrodes were slowly lowered to a depth of 2.5 mm; test stimuli were administered during electrode movement at a rate of 0.05 Hz. The final depths were adjusted until maximal field excitatory post-synaptic potentials (fEPSPs) were obtained; electrodes were allowed to settle for 10 min before baseline recordings were conducted. Baseline measurements were made for 10 min at a stimulus intensity sufficient to produce half-maximal fEPSPs. In all cases baseline stimulation was at a rate of 0.05 Hz.

Unless stated otherwise, all data are expressed as percentage mean change in slope ± S.E.M. of baseline fEPSP. We used *t*-tests (1% level of significance) for either paired samples or independently wherever appropriate.

Protocol used to examine the effect of lipopolysaccharide on baseline stimulation

Field EPSP slopes were recorded for 6 h in both animals injected with LPS or saline.

Protocol used to examine the interaction between lipopolysaccharide and paired-pulse facilitation

For both saline and LPS-treated animals, paired-pulse effects were examined after the baseline was established for a minimum of 10 min. Pairs of stimuli were delivered every 20 s for 50-ms and 100-ms interstimulus intervals (ISIs). The first response and second response elicited by the first and second stimulus of the stimulus pair will be referred to as fEPSP1 and fEPSP2, respectively. These values were chosen because previous experiments[6] demonstrated that PPF was at a maximum in this pathway at 50 ms and its magnitude starts to decrease at the 100 ms interval. The PPF value was calculated by taking the average of slope values of fEPSP1, for a given ISI, and normalising the average of values for fEPSP2 with respect to this value in percentage terms.

Protocol used to examine the interaction between lipopolysaccharide and long-term potentiation

A baseline was initially established in LPS- and saline-injected control animals. Induction of LTP was attempted using high-frequency stimulation (HFS; this consisted of 10 trains of 20 stimuli at 200 Hz, inter-train interval of 2 s; this protocol is identical to that used by Commins *et al.*).[5] Stimulation was resumed at baseline stimulation and fEPSPs were recorded for 1 h. The same protocol was used in saline-treated animals.

Protocol used to examine the interaction between lipopolysaccharide and low-frequency stimulation

A baseline was initially established in LPS- and saline-injected control animals. Low-frequency stimulation (LFS) was then applied (900 pulses at 10 Hz; see Anderson *et al.*).[2] Stimulation was resumed at baseline stimulation and fEPSPs were recorded for 1 h.

After each experiment the rats were overdosed with sodium pentobarbitone and their brains removed and allowed to sink in 4% formaldehyde. All brains were then examined to verify the position of the stimulating and recording electrodes. All data presented here are for stimulating and recording sites that were verified as being in CA1 and the subiculum, respectively. All experiments conformed to the Department of Health (Ireland) regulations and every effort was made to minimise the suffering and the number of animals used.

RESULTS

Temperature control

Body temperature was recorded hourly by a rectal thermometer from both saline- and LPS-injected animals over a 6-h period. There was no significant difference (Independent *t*-test: $t = 0.55$, $\mathrm{df} = 10$, $P > 0.01$) in temperature between the two groups over 6 h.

Effects of lipopolysaccharide and saline on baseline synaptic transmission (six hour)

Responses in saline-treated animals ($n = 4$) remained stable over the recorded period: fEPSPs were 91.4 ± 6.6%, 96.9 ± 5.7%, 100.5 ± 6.7%, 102.2 ± 7.6%, 102.1 ± 3.6% and 107.3 ± 6.6% of the overall mean fEPSP at 1, 2, 3, 4, 5 and 6 h, respectively. In LPS-treated animals ($n = 4$), fEPSP slopes were again recorded over a 6-h period at a stimulation rate of 0.05 Hz. Responses were found to be stable as indicated by the percentage changes in fEPSP slope over this period, which stood at 104.7 ± 4.1%, 106.9 ± 4.3%, 99.65 ± 4.8%, 92.7 ± 7.6%, 96.5 ± 8.2% and 101.1 ± 4.2%, at 1, 2, 3, 4, 5 and 6 h post the commencement of recordings (see Fig. 1). An independent *t*-test ($t = 2.28$, $\mathrm{df} = 116$, $P > 0.01$) confirmed that there were no significant differences in fEPSP responses between the two groups over the 6 h.

Examination of the interaction between paired-pulse facilitation and lipopolysaccharide

Paired-pulse facilitation was examined using 50-ms and 100-ms intervals in both saline- and LPS-treated animals. A strong PPF effect was observed at both intervals for the saline-treated animals ($n = 5$, Fig. 2).

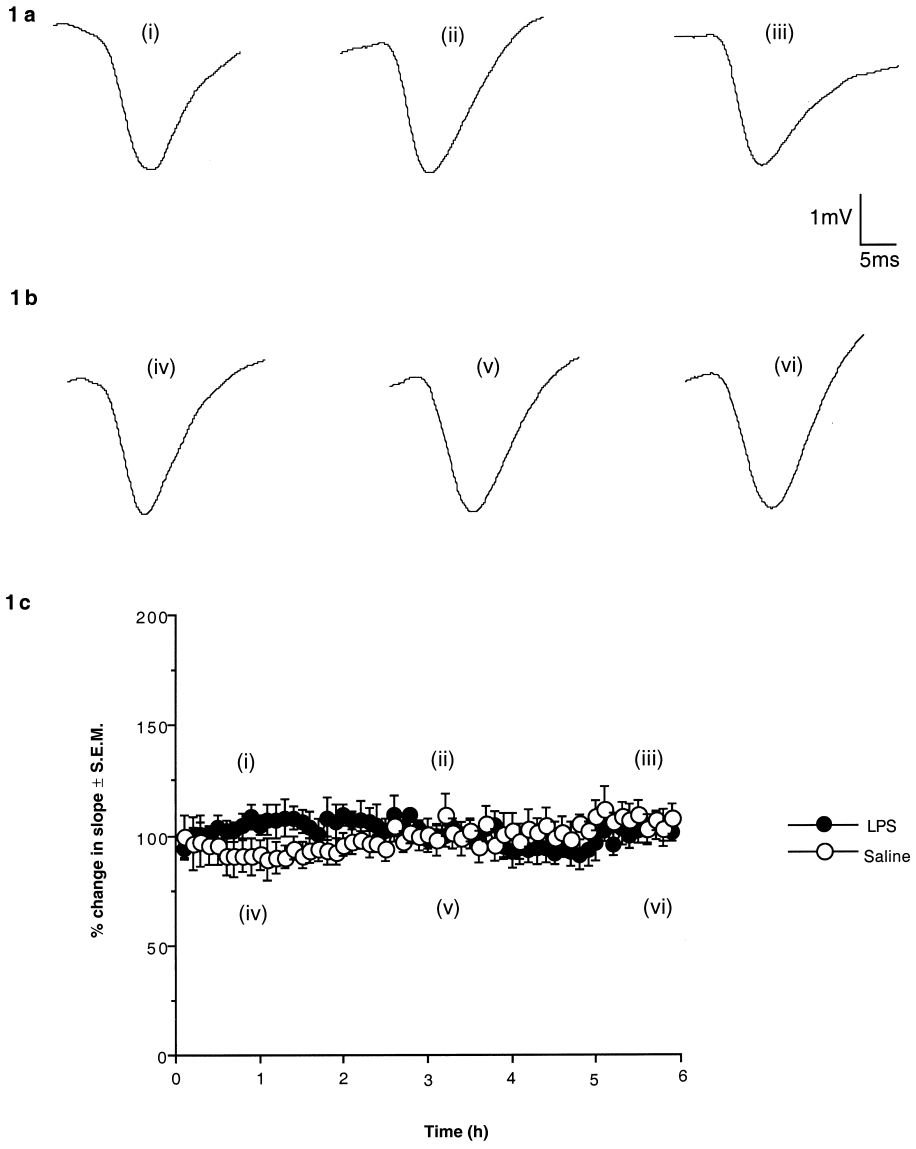

Fig. 1. The effect of lipopolysaccharide (closed circle) and saline (open circle) on synaptic transmission over a 6-h period. No significant differences were noted between the two groups. (a) Sample fEPSP traces taken from saline-treated group. (b) Sample fEPSP traces taken from lipopolysaccharide-treated group; i–vi represent the different points from which the traces were taken in (c).

At 50 ms ISI, fEPSP2 stood at 165.96 ± 14.0% of the value of fEPSP1; at the 100 ms ISI, fEPSP2 stood at 136.19 ± 8% of the value of fEPSP1. A facilitatory effect was also observed in the LPS-treated animals ($n = 5$). The increase in the second response compared to the first was significantly less than that observed in the saline-treated animals. At 50 ms ISI, fEPSP2 stood at 126.8 ± 5.78% of the value of fEPSP1 and at 100 ms ISI, fEPSP2 stood at 115 ± 5.4% of the value of fEPSP1. Independent *t*-tests confirmed that at 50 ms ISI, facilitation was significantly ($t = 2.58$, df = 58, $P = 0.01$) lower in LPS-treated animals than in saline-treated animals. There was no significant decrease in PPF at the 100 ms ISI.

Examination of the interaction between long-term potentiation and lipopolysaccharide

Induction of LTP was attempted using HFS after baseline fEPSP recording. Stimulation was resumed at baseline frequency after HFS and fEPSPs were recorded for 1 h. In saline-treated animals ($n = 6$), LTP was successfully induced and fEPSPs remained potentiated for least 1 h, as indicated by the change in fEPSP slope which stood at 141.3 ± 6.9%, 117.41 ± 4.8%and 115.59 ± 7.8% of baseline immediately, 30 and 60 min post-HFS, respectively (see Fig. 3). Using a repeated measures *t*-test, the final 10 min of the recording period was found have increased significantly when compared to baseline measurements ($t = -10.47$; df = 9; $P < 0.01$). However, in LPS-treated animals ($n = 5$), there was an initial increase in response indicated by fEPSP slopes (121.67 ± 9.15% of baseline; see Fig. 3) but by 60 min post-HFS, the response had returned to baseline levels as indicated by the change in fEPSP slope (99.28 ± 7.42% of baseline). This was confirmed by a paired samples *t*-test which showed no significant differences between the

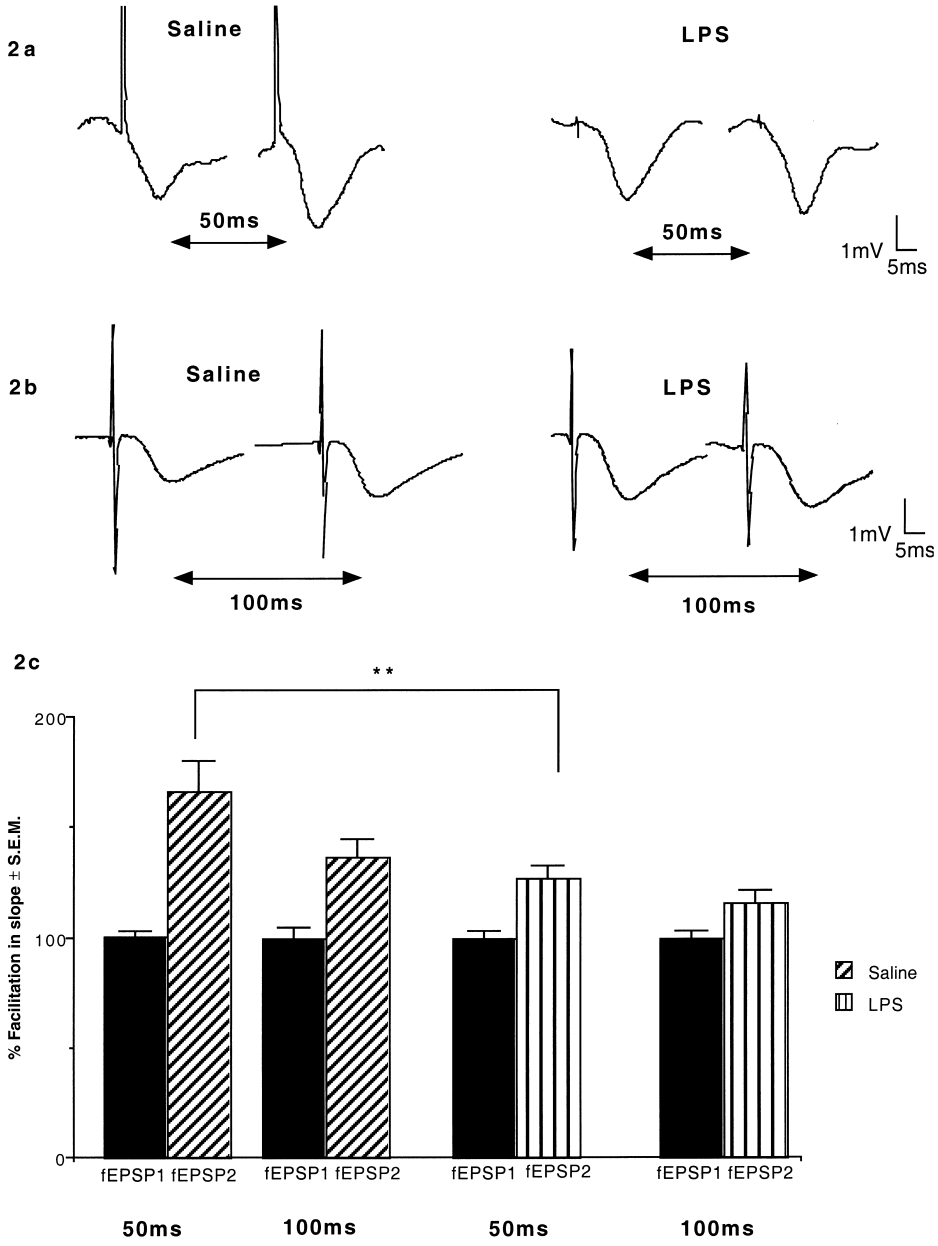

Fig. 2. The effect of lipopolysaccharide and saline on paired-pulse facilitation. (a) Sample fEPSP traces taken from both lipopolysaccharide and saline-treated groups at 50-ms inter-stimulus interval. Note the significantly lower percentage of facilitation in the lipopolysaccharide group. (b) Sample fEPSP traces taken from both lipopolysaccharide and saline-treated groups at 100 ms inter-stimulus interval. (c) A histogram showing the percentage facilitation in both saline-treated (hatched) and lipopolysaccharide-treated (straight lines) at the two inter-stimulus-intervals. Data are nomalised to fEPSP1 (100%).

final 10 min of the recording period and baseline ($t = 2.51$; df = 9; $P > 0.01$). Using an independent *t*-test, a significant difference ($t = -15.81$, df = 18, $P < 0.01$) was found between the final 10 min of LPS-injected animals compared to the final 10 min of saline-injected animals, indicating that LTP was not maintained in the LPS-treated animals.

Examination of the interaction between low-frequency stimulation and lipopolysaccharide

LFS was then applied after baseline fEPSPs were recorded for 10 min. Stimulation was resumed at baseline frequency and fEPSPs were recorded for 1 h. In saline-treated animals ($n = 6$), fEPSPs initially decreased ($95.3 \pm 10.6\%$) immediately following LFS. Responses then recovered and increased slightly ($107.48 \pm 10.5\%$; 10 min post-LFS) and by 60 min post-LFS they had returned to baseline levels, as can be observed in Fig. 4 (response stood at $99.32 \pm 14.35\%$ of baseline 60 min post-LFS). Using a paired-samples *t*-test which compared the baseline responses to responses 60 min post-LFS, no significant differences were found ($t = 0.72$, df = 10, $P > 0.01$) between the two periods, indicating that responses had returned to baseline levels. In LPS-treated animals ($n = 6$), responses also initially decreased

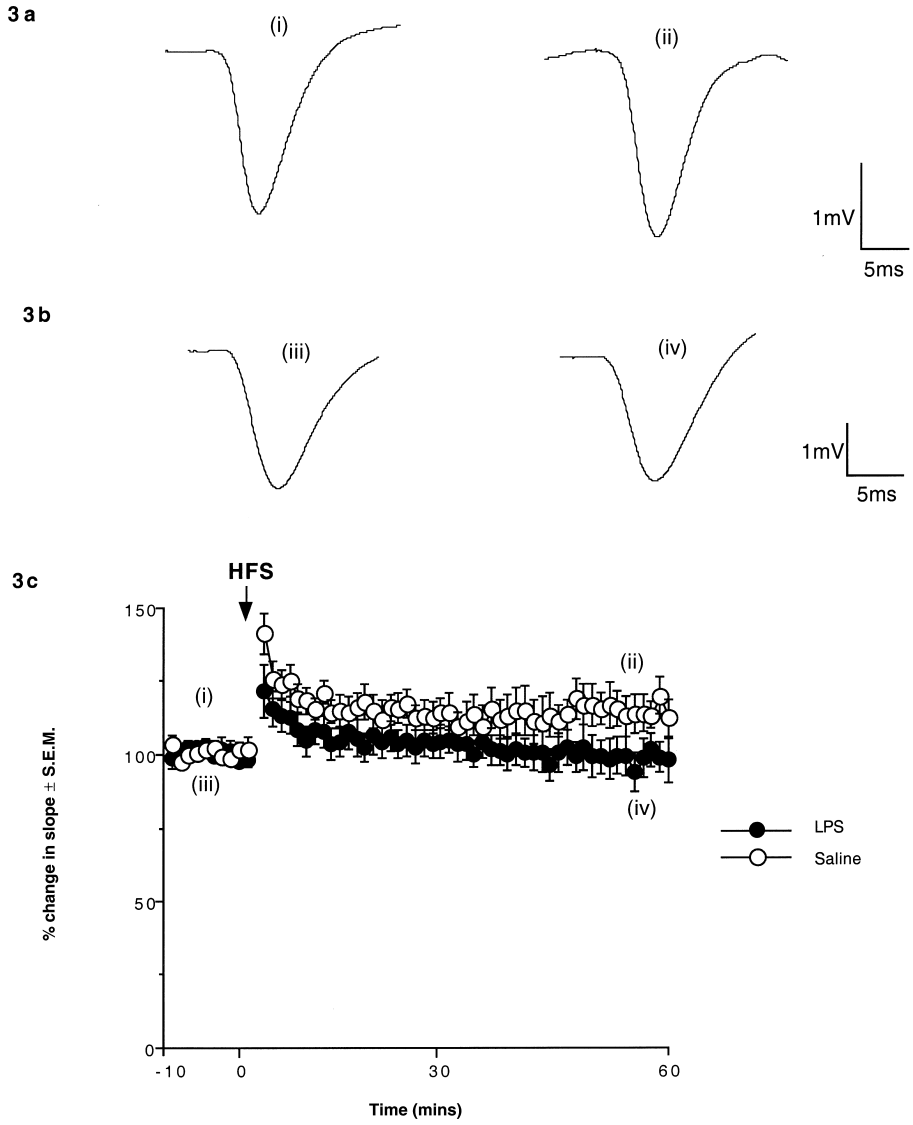

Fig. 3. The effect of lipopolysaccharide (closed circle) and saline (open circle) on long-term potentiation induced by high-frequency stimulation. In saline-injected animals, long-term potentiation was induced but in lipopolysaccharide-injected animals, responses post-stimulation returned to baseline. (a) Sample fEPSP traces taken from saline-treated group. (b) Sample fEPSP traces taken from lipopolysaccharide-treated group; i–iv represent the different points from which the traces were taken in (c).

following LFS (90.5 ± 15.3%). However, responses then recovered and increased (112.1 ± 2.6%) 10 min post-LFS and by 60 min post-LFS, fEPSPs significantly increased as can be observed in Fig. 4 (response stood at 110.96 ± 5.2% of baseline). A paired sample *t*-test ($t = -14.0$, df = 8, $P < 0.01$) revealed that the final 10-min recording period had significantly increased when compared to baseline responses. Using an independent *t*-test, responses of the final 10 min of LPS-injected animals had significantly increased when compared to the final 10 min of saline-injected animals ($t = 7.76$; df = 18; $P < 0.01$).

DISCUSSION

We examined the effects of LPS on synaptic transmission and plasticity in the subiculum *in vivo*, an area critical in learning and memory,[21] and which may also play a role in the mediation of stress responses as a result of the high density of IL-1 receptors[3] and glucocorticoid receptors[25] located in the hippocampal formation. The effects of LPS are mediated primarily through the release of cytokines such as IL-1.[10] The effect of LPS on body temperature was examined and we found no significant difference between the groups; the temperature, however, was very variable and we only took recordings every hour. We also were unable to find a significant difference in baseline synaptic transmission between treated and control animals over a 6-h period. A similar finding has been reported in the dentate gyrus *in vitro* with IL-1 beta. Coogan and O'Connor[8] suggest that perfusion with IL-1 beta for up to 2 h had no significant effect on low frequency evoked dual AMPA–NMDA component EPSP.

There has been little research carried out to examine the effect of either IL-1 or LPS on paired-pulse facilitation

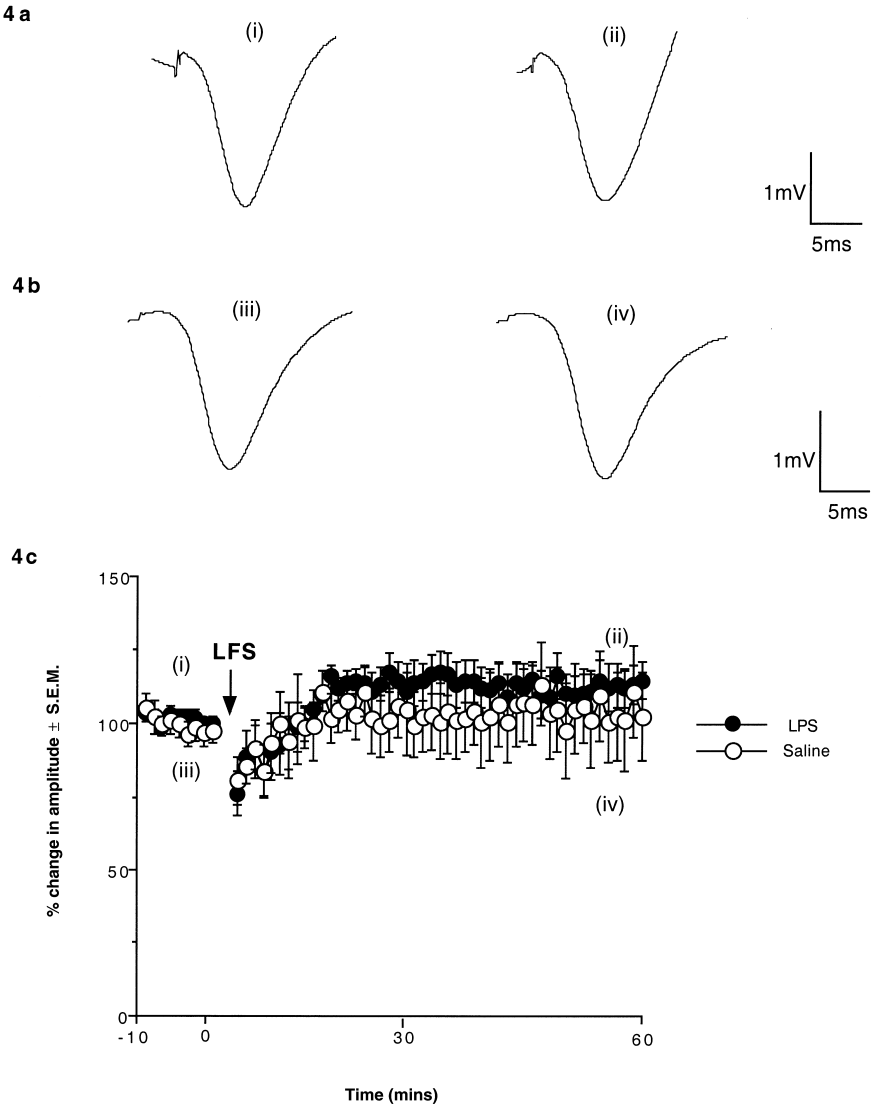

Fig. 4. The effect of lipopolysaccharide (closed circle) and saline (open circle) on responses following low-frequency stimulation. A small potentiation was observed in lipopolysaccharide-treated animals. (a) Sample fEPSP traces taken from saline-treated group. (b) Sample fEPSP traces taken from lipopolysaccharide-treated group; i–iv represent the different points from which the traces were taken in (c).

(considered to be a short-term plastic phenomenon). However, one study hints that the PPF effect may be susceptible to endotoxin challenge. Coogan and O'Connor[8] suggest that pre-treatment with IL-1 beta blocks the decreases in paired-pulse depression at certain ISIs following tetraethylammonium-induced long-term potentiation in the dentate gyrus. We found that the paired-pulse facilitation in the CA1-subiculum pathway was significantly lower in LPS-injected animals than control animals at shorter rather than longer ISIs. This effect may be due to increased inhibition in LPS-treated animals resulting from higher levels of IL-1. Indeed it has been demonstrated that IL-1 beta enhances and prolongs synaptic inhibition up to two- or three-fold in area CA1.[32] PPF is thought to be pre-synaptic in origin, resulting from a transient increase in calcium levels in the presynaptic terminal from the first stimulus, elevating the response to the second stimulus.[30,33] The finding that the facilitatory effect is reduced in LPS-treated animals may suggest a pre-synaptic role for the action of LPS; it may be that LPS blocks the uptake of pre-synaptic calcium. Given that the effect of LPS on PPF is time-dependent, it may be that LPS affects the buffering of presynaptic Ca^{++} or slows down the mobilisation of presynaptic neurotransmitter vesicles in response to presynaptic stimulation. However, the intracellular mechanisms of action of LPS and indeed interleukins on synaptic transmission and plasticity remain complex and obscure.

LTP has been considered as a biological substrate for learning and memory.[19] Previous research has indicated that LTP induction can be inhibited by IL-1 beta in both areas CA1 and CA3 of the hippocampus.[4,14] In the dentate gyrus of the rat *in vitro*, a role for this cytokine in synaptic plasticity has also been suggested.[9] IL-1 beta inhibits induction of LTP in the dentate gyrus of slices; this effect is attenuated by the interleukin-1 receptor

antagonist IL-1ra.[10] Furthermore, a recent study has found that blockade of IL-1 receptors by IL-1ra resulted in a reversible impairment of LTP maintenance but not its induction,[26] indicating that this cytokine may have a more subtle role to play in synaptic plasticity than previously thought. IL-1 beta may have an effect by enhancing and prolonging synaptic inhibition, which has been suggested for hippocampal pyramidal cells of the CA1 region.[32] Few studies have examined the role of LPS on synaptic plasticity. Cunningham *et al.*[10] demonstrate that the effect of IL-1 beta on LTP is mimicked by LPS in the dentate gyrus. These authors further suggest that Il-1ra can antagonise the LPS effect. Although LPS causes the release of IL-1, LPS may have a direct effect on synaptic plasticity due to its rapid action.[10] There is also evidence that endotoxins may have an effect on certain neurotransmitters such as noradrenaline or serotonin. Wang and White,[28] for example, have shown that when LPS is applied to parietal cortical slices, there is a sustained release of noradrenaline and other neurotransmitters which may be linked to an increase in excitation in the brain. Furthermore, whereas LPS has only a minor effect on hippocampal noradrenaline, LPS causes a large increase in extracellular serotonin in the hippocampus.[17] An increase in serotonin may improve the ability of an organism to cope with stress.[20] Experiments presented in this paper demonstrate for the first time that LPS can also prevent LTP in the CA1-subiculum pathway *in vivo*. The effects of LPS appear to occur in a frequency-dependent fashion. Very low rates of stimulation (0.05 Hz) have no effect on synaptic transmission; intermediate levels of stimulation (up to 10 Hz) cause a moderate increase in the amplitude and slope of fEPSPs, and high rates (100 Hz) have a transient effect on synaptic transmission. Whether the inability to produce LTP is due to a direct action of LPS or indirectly via the release of interleukins causing an increase in inhibition is unclear. This finding, however, has important implications for learning and memory and future experiments should examine the behavioural consequences of LPS, and in particular the effect of LPS on hippocampal-dependent learning tasks.

Immune system stimulation such as that provided by LPS has been reported to increase immunoreactivity and it has been suggested that LPS has similar effects to those produced by stress.[22] Long-term depression (LTD) can be attained in area CA1 if an animal is stressed for 30 min prior to anaesthesia and a low-frequency stimulation is applied.[31] We have also found depression of synaptic transmission in the subiculum *in vivo*, following stress and LFS.[7] By contrast, the present experiments demonstrate that LFS combined with LPS causes a small but significant increase in synaptic transmission in the CA1-subiculum pathway. This finding suggests that there are subtle interactions between low-frequency stimulation protocols, behavioural stress and LPS.

Acknowledgements—This work was supported by the Wellcome Trust, the European Commission, the HEA/Enterprise Ireland and Provost's Fund of Trinity College. We would like to thank Michael Anderson and Kendra Shaw (Department of Psychology, Trinity College) and especially Marina A. Lynch (Department of Physiology, Trinity College) for helpful discussions.

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(*Accepted* 18 *October* 2000)