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Interleukin-1β inhibits a tetraethylammonium-induced synaptic potentiation in the rat dentate gyrus in vitro

Andrew N. Coogan, John J. O'Connor *

Department of Human Anatomy and Physiology, University College, Earlsfort Terrace, Dublin 2, Ireland

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Abstract

The effect of the pro-inflammatory cytokine, interleukin-1β on an NMDA receptor-independent form of synaptic plasticity brought about by the application of the K^+ channel blocker tetraethylammonium, was examined in the rat dentate gyrus in vitro. Field excitatory postsynaptic potentials (EPSPs) were recorded from the medial perforant path of the dentate gyrus every 20 s. Perfusion of the K^+ channel blocker, tetraethylammonium chloride (25 mM) for 10 min and subsequent washout gave rise to robust and long-term potentiation of the field EPSP slope (tetraethylammonium induced long-term potentiation; $125 \pm 5\%$ of baseline 60 min following tetraethylammonium-washout; $n = 7$, $P < 0.05$) Application of interleukin-1β (1 ng/ml) for 30 min was found to inhibit the induction, but not the maintenance of the tetraethylammonium induced long-term potentiation ($n = 8$). Heat denatured interleukin-1β had no effect on tetraethylammonium induced long-term potentiation ($n = 6$). The expression of tetraethylammonium induced long-term potentiation was found to be accompanied by an increase in the magnitude of paired pulse depression seen at interstimulus intervals of 20 and 100 ms (controls, $42 \pm 5\%$ and $13 \pm 2\%$; tetraethylammonium, $62 \pm 5\%$ and $22 \pm 2\%$ respectively for both intervals; $n = 6$, $P < 0.05$). The increase in paired pulse depression at an interstimulus interval of 100 ms was significantly attenuated by pre-treatment of slices with interleukin-1β. The inhibitory effect of interleukin-1β on both tetraethylammonium induced long-term potentiation and the tetraethylammonium induced increase in paired pulse depression was antagonised by pre-incubation with the interleukin-1 receptor antagonist. Interleukin-1 receptor antagonist was found to have no effect on tetraethylammonium induced long-term potentiation when applied on its own ($n = 5$). The p38 mitogen activated protein kinase inhibitor SB203580 (4-(4-fluorophenyl)-2-(4 methylesulfinylphenyl)-5-(4-pyridyl)1H-imidazole) was also found to inhibit the induction of tetraethylammonium induced long-term potentiation ($n = 6$). These findings suggest a possible role for interleukin-1β in the modulation of NMDA receptor-independent synaptic plasticity in the rat dentate gyrus.

Keywords: Long-term potentiation; Interleukin-1; MAP kinases; SB203580

1. Introduction

The pro-inflammatory cytokine interleukin-1β has been shown to be produced in the central nervous system in response to a number of stimuli, such as peripheral lipopolysaccharide (Laye et al., 1994), traumatic brain injury (Fan et al., 1995), acute stress (Nguyen et al., 1998) and to exert a number of neuromodulatory effects therein (Rothwell and Hopkins, 1995). Interleukin-1 receptors and their accessory proteins have also been shown to be widely distributed in the central nervous system (Ericsson et al., 1995) with particularly high levels present in the hippocampus (Takao et al., 1990; Ban et al., 1991; Parnet et al., 1994; Liu et al., 1996). The presence of interleukin-1β and interleukin-1 receptors in hippocampus, and the inhibition of spatial learning by interleukin-1β (Oitzl et al., 1993) have lead to the investigation of the effects of interleukin-1β on long-term potentiation, a use-dependent, long-lasting increase in synaptic efficacy which is thought to be an important underlying mechanism of learning and memory (Bliss and Collingridge, 1993).

Pre-incubation of hippocampal slices with interleukin-1β at pathophysiological concentrations has previously been shown to inhibit tetanically induced and NMDA receptor-dependent forms of long-term potentiation in the CA1

* Corresponding author. Tel.: +353-1-706-7263; Fax: +353-1-706-7417; E-mail: john.oconnor@ucd.ie

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(Bellinger et al., 1993) and the dentate gyrus (Cunningham et al., 1996; Coogan and O'Connor, 1997) and also to inhibit an NMDA receptor-independent tetanically induced long-term potentiation in the mossy fibre-CA3 pathway (Katuski et al., 1990). The molecular mechanisms underlying the interleukin-1β induced inhibition of long-term potentiation remain obscure, although a depression of voltage-dependent Ca^{2+} currents in the CA_1 via a protein kinase C dependent mechanism (Plata-Salaman and ffrench-Mullen, 1992, 1994) and an inhibition of NMDA receptor mediated potentials in the dentate gyrus (Coogan and O'Connor, 1997) may be involved. Further studies have indicated that activation of the p38 mitogen activated protein (MAP) kinase is necessary to mediate interleukin-1β's actions on long-term potentiation and NMDA receptor potentials in the dentate gyrus (Coogan et al., 1999b). To further investigate the action of interleukin-1β on long-term potentiation in the dentate gyrus we utilised a form of NMDA receptor-independent synaptic potentiation brought about by application of the K^+ channel blocker tetraethylammonium (Aniksztejn and Ben-Ari, 1991; Coogan et al., 1999a). We also investigated the action of tetraethylammonium and interleukin-1β on paired pulse depression in the dentate gyrus. Paired pulse depression of the second synaptic response to paired stimuli in the medial perforant path has been well characterised across a broad range of interstimulus intervals and is believed to primarily reflect changes in pre-synaptic function (Kahle and Cotman, 1993).

Our results suggest that interleukin-1β can inhibit the induction, but not the maintenance, of this NMDA receptor-independent form of long-term potentiation in the dentate gyrus via a mechanism that seems to be dependent on activation of the p38 MAP kinase cascade.

2. Materials and methods

2.1. Recording of field excitatory postsynaptic potentials

Transverse hippocampal slices were prepared from male Wistar rats (70–150 g) as previously described (Coogan et al., 1999a). Briefly, under anaesthesia with chloroform, the brain was rapidly removed and hippocampal slices (350 μm) were prepared using a Campden vibroslice. Slices were then equilibrated for at least 1 h at room temperature in oxygenated (95% O_2, 5% CO_2) artificial cerebrospinal fluid (composition in mM: NaCl, 120; KCl, 2.5; $MgSO_4$, 2; $CaCl_2$, 2; $NaHCO_3$, 26; NaH_2PO_4, 1.25; D-glucose, 10) before being transferred to a recording chamber maintained at 29–31°C and being perfused with artificial cerebrospinal fluid at a flow rate of 5–7 ml/min.

Field excitatory postsynaptic potentials were evoked by stimulation of the medial perforant pathway with a glass monopolar electrode and responses were recorded with a glass electrode (1–5 MΩ) placed in the middle third of the molecular layer of the dentate gyrus (both approximately 100 μm from the granule cell layer). Stimulation of the medial perforant pathway was confirmed by the presence of paired-pulse depression (McNaughton, 1980). Stimulus strength was adjusted to give a response of ~33% of maximal, and delivered at 0.05 Hz. All experiments were carried out in the presence of 100 μM of the $GABA_A$ receptor antagonist picrotoxin. Responses were acquired off line and analysed on a PC using the Strathclyde Electrophysiology Software (Dr. John Dempster).

2.2. Data analysis

The postsynaptic response was expressed as the slope of the field excitatory postsynaptic potentials (EPSPs) (first 1 ms; mV/ms), averaged in 5 min bins and then normalised to the average baseline value. Paired-pulse depression was quantified by the following equation: $\{(S_1 - S_2)/S_1\} \times 100$.

All results are quoted as mean ± S.E.M. Statistical analysis was performed using paired, two-tailed Student's *t*-test for comparison between baseline and post-treatment values and two tailed unpaired Student's *t*-test used for comparisons between control and test slices. The difference was considered significant if $P < 0.05$.

2.3. Drugs

Human recombinant interleukin-1β and interleukin-1 receptor antagonist were obtained from R&D Systems Europe, reconstituted in sterile phosphate buffered saline containing 0.2% w/v bovine serum albumin before being diluted in artificial cerebrospinal fluid to the desired working concentration of 1 ng/ml for interleukin-1β and 50 ng/ml for interleukin-1 receptor antagonist. SB203580 (4-(4-fluorophenyl)-2-(4 methylesulfinylphenyl)-5-(4-pyridyl)1H-imidazole) was obtained from Alexis and was dissolved in dimethyl sulphoxide to a final concentration of 0.4% v/v. Tetraethylammonium was obtained from Sigma UK and all other salts from British Drug House. In some experiments to control for possible contamination of interleukin-1β sample by endogenous endotoxin, samples were heated to 90°C for 30 min to denature protein but not heat-stable lipopolysaccharide.

3. Results

3.1. Interleukin-1β inhibits tetraethylammonium-induced synaptic potentiation

As previously reported (Coogan et al., 1999b), treatment of slices with tetraethylammonium (25 mM) for 10 min led to a depression of the field EPSP slope, followed by a potentiation after washout of tetraethylammonium

(tetraethylammonium induced long-term potentiation; 125 ± 5% of baseline 1 h after tetraethylammonium washout; $n = 7$; $P < 0.05$ compared to original baseline; Fig. 1). This represented an average field EPSP slope of 1.26 ± 0.08 mV/ms before tetraethylammonium application and an increase to 1.58 ± 0.06 mV/ms 1 h after tetraethylammonium washout. Pre-treatment of slices with interleukin-1β (1 ng/ml) for 30 min prior to and during tetraethylammonium treatment inhibited the tetraethylammonium induced long-term potentiation without affecting normal baseline transmission (90 ± 5%, 1 h following tetraethylammonium washout; $n = 8$; $P < 0.01$ compared to slices treated with tetraethylammonium alone; Fig. 1).

Perfusion of interleukin-1β during the maintenance phase of tetraethylammonium induced long-term potentiation had no further effect on the field EPSP slope (118 ± 4%; $n = 6$; Fig. 2A). To control for possible effects of contaminating heat stable endotoxin in the interleukin-1β, aliquots of interleukin-1β were heated to 90°C for 30 min to denature the protein. Slices treated with the denatured samples showed no inhibition of tetraethylammonium induced long-term potentiation (120 ± 3%, 1 h following tetraethylammonium-washout; $n = 6$; Fig. 2B).

3.2. Changes in paired-pulse depression following induction of tetraethylammonium induced long-term potentiation

Following the induction of tetraethylammonium induced long-term potentiation there was a significant increase in the magnitude of paired-pulsed depression measured at interstimulus intervals of 20 and 100 ms. At a 20 ms interval paired pulse depression was increased from 42 ± 5% pre-tetraethylammonium treatment to 62 ± 5%, 1 h post-tetraethylammonium washout ($P < 0.01$ between

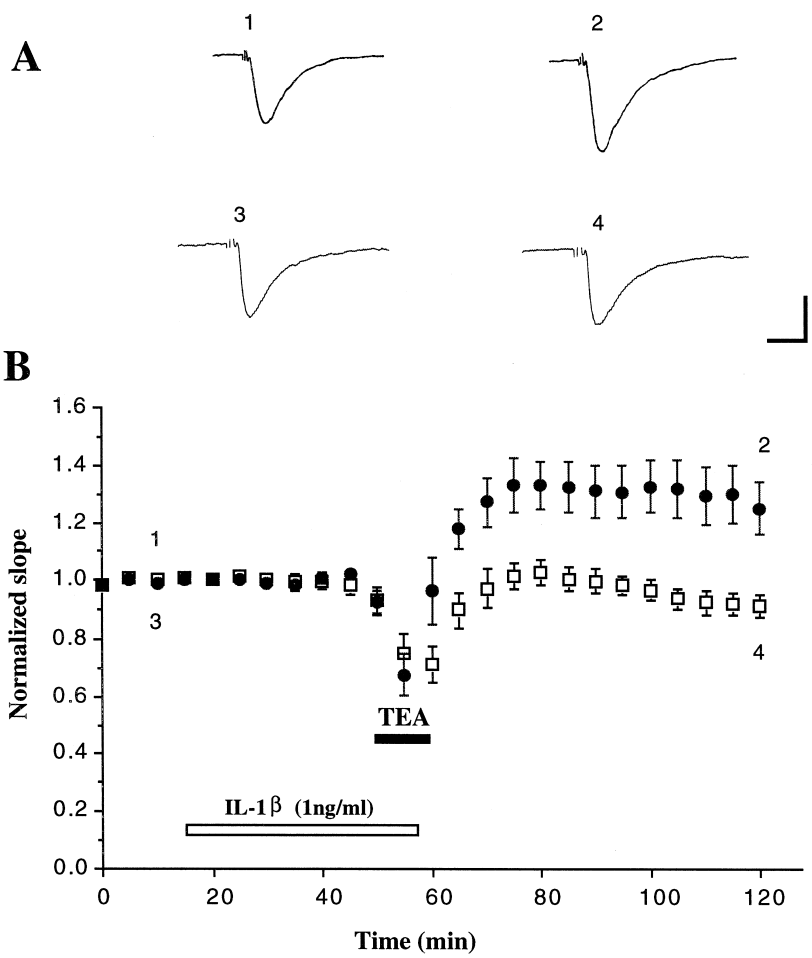

Fig. 1. Interleukin-1β inhibits the induction of tetraethylammonium (TEA) induced long-term potentiation. (A) Representative traces of the averages of ten field EPSPs. Traces 1 and 2 are from the control slice, before applying and after washout of tetraethylammonium (25 mM). Traces 3 and 4 are from the test slice, before any drug and after washing out of tetraethylammonium which was applied in the presence of interleukin-1β (1 ng/ml). For clarity the stimulus artefacts have been partially removed. Bar: 1 mV vertical; 5 ms horizontal. (B) Time course showing the effects of tetraethylammonium application on field EPSP slope in control slices (●; $n = 7$) and in slices treated with interleukin-1β (□; $n = 8$). Pre-treatment of slices with interleukin-1β (1 ng/ml; open bar) significantly inhibited the induction of tetraethylammonium induced long-term potentiation (125 ± 5% 1 h following tetraethylammonium-washout in control slices; 90 ± 4% 1 h following tetraethylammonium-washout in interleukin-1β treated slices; $P < 0.01$). All points are the mean ± S.E.M.

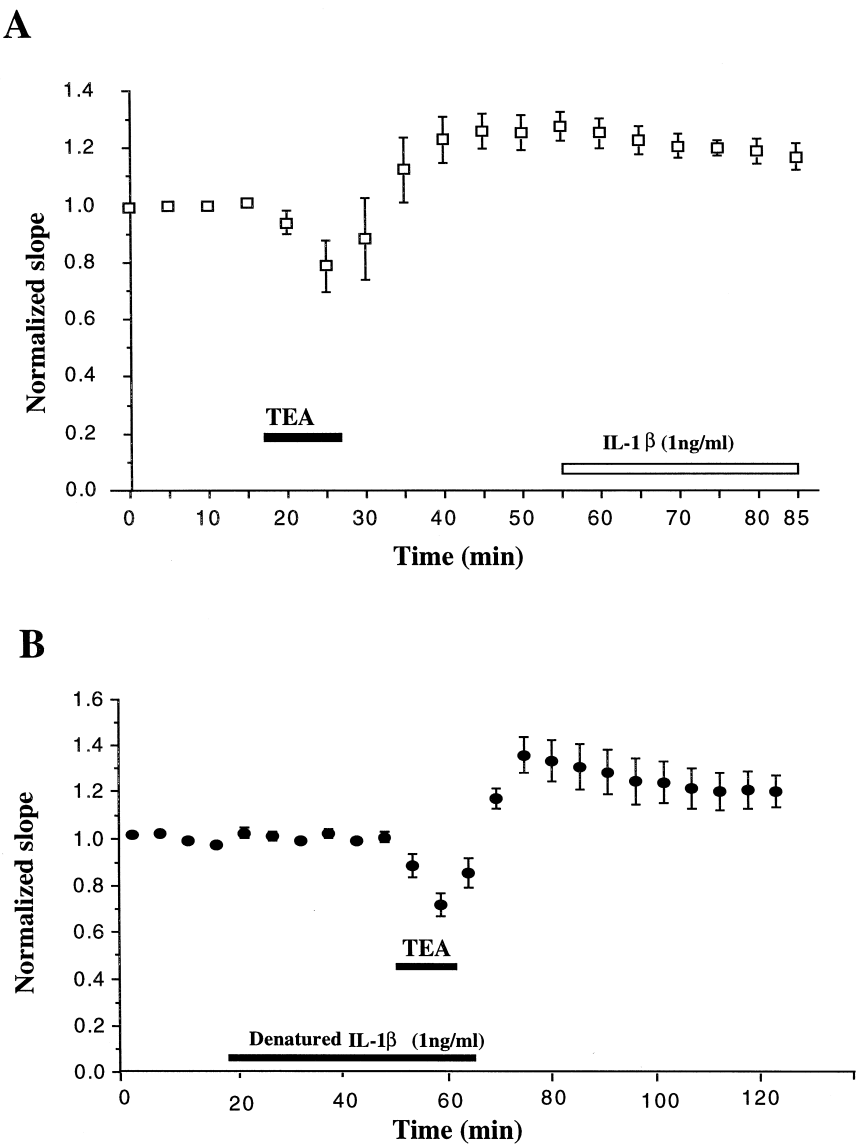

Fig. 2. Interleukin-1β does not affect the maintenance of tetraethylammonium (TEA) induced long-term potentiation and heat denatured interleukin-1β has no effect on tetraethylammonium induced long-term potentiation. (A) Application of interleukin-1β (1 ng/ml) 30 min following the establishment of tetraethylammonium induced long-term potentiation does not affect the maintenance of the potentiation (118 ± 4% at 1 h following tetraethylammonium-washout; $n = 6$). (B) The application of heat-denatured interleukin-1β does not inhibit the induction of tetraethylammonium induced long-term potentiation (120 ± 3% 1 h following tetraethylammonium-washout; $n = 6$), suggesting that the action of interleukin-1β on tetraethylammonium induced long-term potentiation is not due to contaminating, heat stable endotoxin. All points are the mean ± S.E.M., $n = 6$).

pre and post-tetraethylammonium values; $n = 8$; Fig. 3A + B). At a 100 ms interval paired pulse depression increased from 13 ± 2% in controls to 22 ± 2% 1 h following tetraethylammonium-washout ($n = 7$; $P < 0.05$; Fig. 3B).

Since the tetraethylammonium induced increase in the slope of the conditioning field EPSP may itself cause an increase in paired pulse depression, in four experiments the stimulus voltage was reduced to give field EPSP slope values approximately equal to pre-tetraethylammonium values. In these experiments tetraethylammonium application also significantly increased paired pulse depression at both 20 and 100 ms interstimulus interval (38 ± 6% to 56 ± 6% and 15 ± 3% to 21 ± 3%, respectively, $n = 4$, $P < 0.05$ for both).

Application of interleukin-1β on its own had no effect on paired pulse depression at 20 or 100 ms intervals. In the presence of interleukin-1β the tetraethylammonium-induced increase in paired pulse depression at 20 ms interval was not inhibited (36 ± 5% vs. 47 ± 5%; $n = 8$; $P < 0.05$; Fig. 3B). However at 100 ms interval, treatment of slices with interleukin-1β significantly attenuated the changes in paired pulse depression seen following tetraethylammonium-treatment (9 ± 2% vs. 14 ± 3%; NS; $n =$ 8). In experiments where the effect of interleukin-1β on tetraethylammonium induced long-term potentiation and

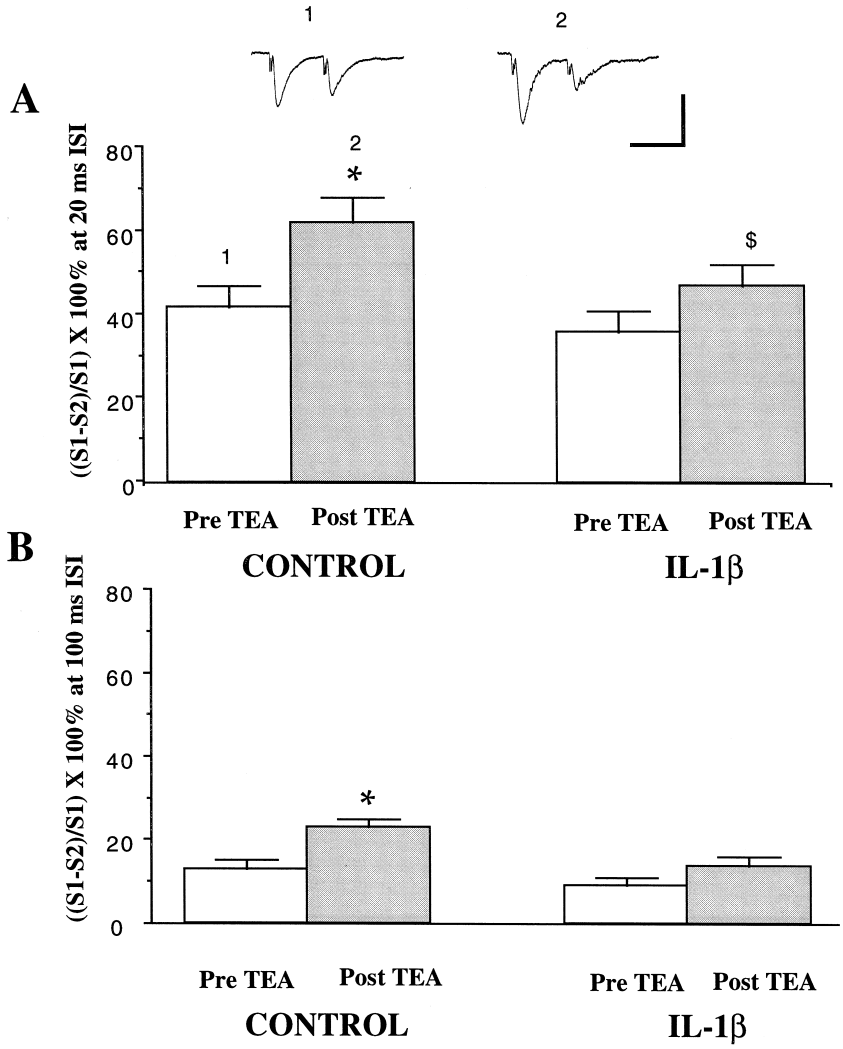

Fig. 3. Tetraethylammonium (TEA) induced long-term potentiation is accompanied by an increase in paired-pulse depression. (A) Histograms summarising the changes in paired pulse depression at interstimulus interval of 20 ms in control and interleukin-1β (1 ng/ml) treated slices. Tetraethylammonium led to an increase in the magnitude of paired pulse depression in controls. This effect was not significantly inhibited by interleukin-1β. Insets are representative field EPSP traces showing examples of paired-pulse depression at 20 ms interval (1) prior to tetraethylammonium application and (2) 1 h following tetraethylammonium-washout. Bar: vertical, 1 mV; horizontal, 20 ms. (B) Histogram summarising the changes in paired pulse depression at interstimulus interval of 100 ms in control and interleukin-1β treated slices. Tetraethylammonium lead to a significant increase in paired pulse depression in controls. This effect was significantly reversed by pre-treatment with interleukin-1β. All bars are the mean ± S.E.M.; $n = 8$. ($^{*}P < 0.05$ compared to pre-tetraethylammonium in controls; $^{\$}P < 0.05$ compared to pre-tetraethylammonium in IL-1β treated slices).

tetraethylammonium induced changes in paired pulse depression were carried out, no correlation was observed between the magnitude of tetraethylammonium induced long-term potentiation and the increase in paired pulse depression ($n = 3$).

3.3. Interleukin-1 receptor antagonist blocks the effects of interleukin-1β

Treatment of slices with the Interleukin-1 receptor antagonist (50 ng/ml), a naturally occurring, highly specific antagonist of interleukin-1 receptors, was found to have no effect on the induction of tetraethylammonium induced long-term potentiation on its own (120 ± 3% at 1 h after tetraethylammonium washout; $n = 4$; Fig. 4A). Pre-treatment of slices with interleukin-1 receptor antagonist at 50 ng/ml for 30 min prior to interleukin-1β (1 ng/ml) perfusion, significantly attenuated the interleukin-1β induced inhibition of tetraethylammonium induced long-term potentiation (123 ± 4% 1 h following tetraethylammonium-washout; $n = 5$; $P < 0.05$ for interleukin-RA + interleukin-1β vs. interleukin-1β alone; Fig. 4B). The interleukin-1β inhibition of the increase in paired pulse depression seen during tetraethylammonium induced long-term potentiation was reversed by interleukin-1 receptor antagonist (for interleukin-1 receptor antagonist + interleukin-1β, paired pulse depression was 60 ± 4% and 22 ± 3% for 20 and 100 ms intervals, respectively, 1 h post-

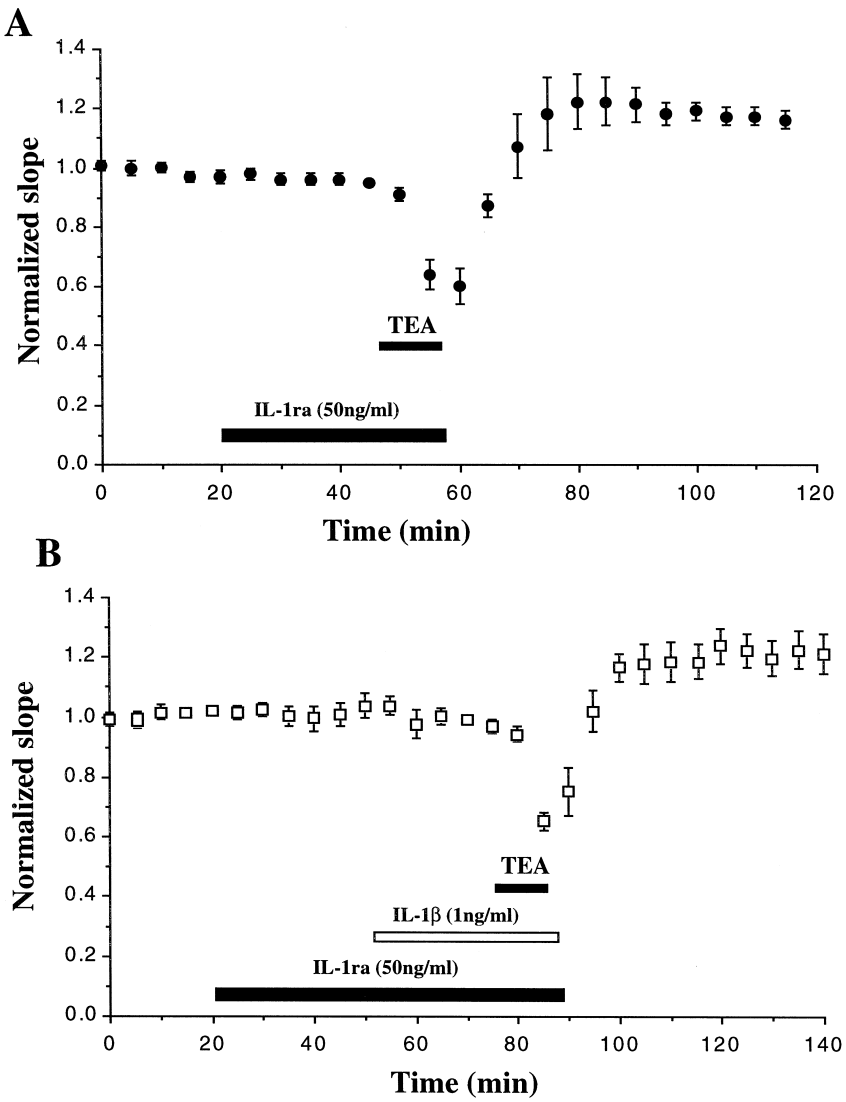

Fig. 4. Interleukin-1 receptor antagonist reverses the inhibitory effect of interleukin-1β (1 ng/ml) on tetraethylammonium (TEA) induced long-term potentiation. (A) Time course of the effect of interleukin-1 receptor antagonist on tetraethylammonium induced long-term potentiation. Interleukin-receptor antagonist (50 ng/ml) had no effect on baseline synaptic transmission and tetraethylammonium induced long-term potentiation when applied on its own (tetraethylammonium induced long-term potentiation was $120 \pm 3\%$ at 1 h following tetraethylammonium washout; $n = 4$). (B) Treatment of slices with interleukin-1 receptor antagonist (50 ng/ml) for 30 min prior to and during interleukin-1β perfusion antagonised the inhibitory effect of interleukin-1β on tetraethylammonium induced long-term potentiation (tetraethylammonium induced long-term potentiation in the presence of both interleukin-1 receptor antagonist and interleukin-1β was $123 \pm 4\%$ at 1 h following tetraethylammonium washout; $n = 5$).

tetraethylammonium compared to $47 \pm 5\%$ and $14 \pm 3\%$ in interleukin-1β alone; $n = 5$; $P < 0.05$ for both). Interleukin-1 receptor antagonist itself did not affect paired pulse depression.

3.4. The p38 MAP kinase inhibitor, SB203580 blocks the induction of tetraethylammonium induced long-term potentiation

Bath perfusion of slices with the p38 MAP kinase inhibitor, SB203580 (1 μM) had no significant effect on baseline field EPSP slope ($n = 6$). However application of SB203580 60 min prior to tetraethylammonium application significantly reduced the tetraethylammonium-induced potentiation ($91 \pm 3\%$ 1 h following tetraethylammonium-washout; $n = 6$; $P < 0.01$ compared to slices treated solely with tetraethylammonium; Fig. 5). Interestingly and unlike interleukin-1β, SB203580 had no significant effect on the tetraethylammonium-induced increase in paired pulse depression (1 h following tetraethylammonium-washout in the presence of SB203580 paired pulse depression was $51 \pm 4\%$ and $25 \pm 3\%$ for 20 ms and 100 ms intervals respectively; $n = 6$; not significant compared to slices treated solely with tetraethylammonium). The vehicle for SB203580, dimethyl sulphoxide (0.4% v/v) when per-

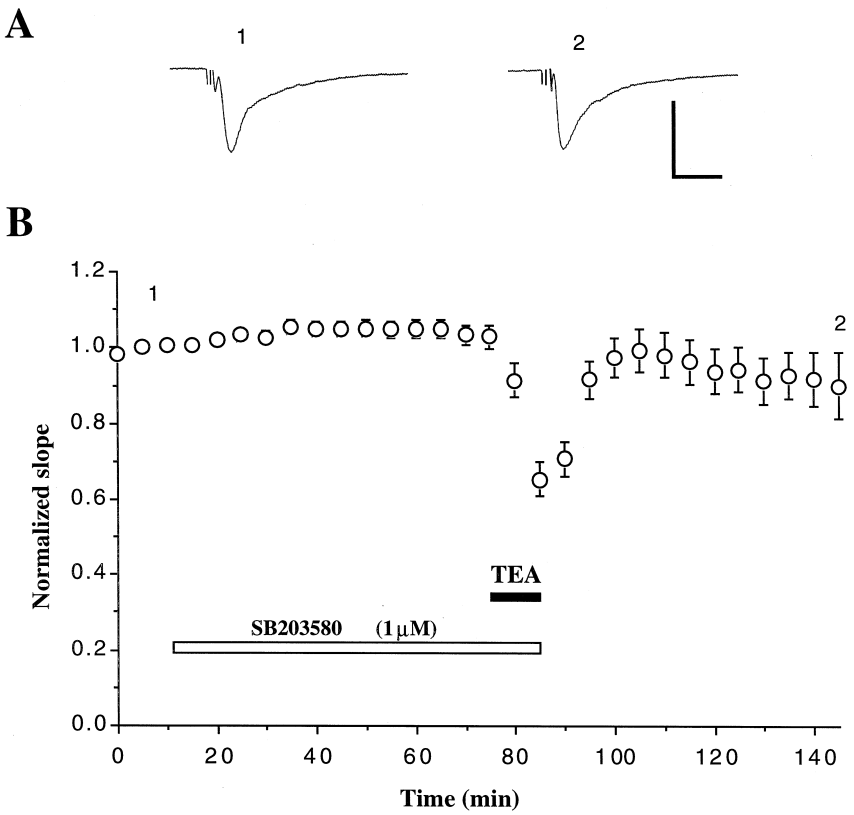

Fig. 5. The p38 MAP kinase inhibitor SB203580 blocks the induction of tetraethylammonium (TEA) induced long-term potentiation. (A) Representative traces of the average of 10 records taken (1) prior to SB203580 and tetraethylammonium treatment and (2) 1 h following tetraethylammonium and SB203580 washout. Bar: vertical, 1 mV; horizontal, 5 ms. (B) Time course of the effects of SB203580 (1 μM) on tetraethylammonium induced long-term potentiation. Treatment of slices with SB203580 blocked the subsequent induction of any synaptic potentiation following tetraethylammonium treatment ($91 \pm 3\%$ 1 h following tetraethylammonium-washout; $n = 6$).

fused onto the slices alone had no significant effect on baseline field EPSP amplitude or tetraethylammonium induced long-term potentiation ($n = 4$; $129 \pm 7\%$ compared to $125 \pm 5\%$ in controls).

4. Discussion

The data presented in this paper shows an inhibitory effect of interleukin-1β on a synaptic potentiation induced by application of the K^+ channel blocker tetraethylammonium in the rat dentate gyrus in vitro. This synaptic potentiation has previously been characterised in the dentate gyrus and shown to be insensitive to the NMDA receptor antagonist D-AP5 (D-2-amino-5-phosphonopentanoate), the L-type voltage-dependent Ca^{2+} channel blocker nifedipine, but sensitive to the metabotropic glutamate receptor antagonist, α-methyl-4-carboxy-phenyl glycine and the low-voltage activated Ca^{2+} channel blocker nickel (Coogan et al., 1999a). Picrotoxin was included in the artificial cerebrospinal fluid in all experiments to block $GABA_A$ mediated inhibitory postsynaptic potentials. In the absence of $GABA_A$ receptor block the induction of long-term potentiation can be impaired in the dentate gyrus unlike the CA1 region (unpublished results).

The fact that the tetraethylammonium-induced potentiation appeared to be NMDA receptor independent made it an interesting model in which to examine the effects of interleukin-1β, as interleukin-1β has previously been shown to inhibit NMDA receptor dependent tetanically induced long-term potentiation in the dentate gyrus (Cunningham et al., 1996), possibly through inhibition of NMDA receptor function (Coogan and O'Connor, 1997). It has also been postulated that Ca^{2+} entry into hippocampal neurones through voltage dependent Ca^{2+} channels and NMDA receptor channels leads to activation of separate biochemical cascades (Cavus and Teyler, 1996). This may suggest that the biochemical pathways underlying expression of tetraethylammonium induced long-term potentiation may differ from those underlying expression of tetanically induced long-term potentiation (Gallin and Greenberg, 1995).

As previously reported (Cunningham et al., 1996; Coogan and O'Connor, 1997) interleukin-1β at the pathophysiological concentration of 1 ng/ml had no effect on baseline synaptic transmission under standard recording conditions. However, when slices were preincubated with

interleukin-1β for 30 min prior to tetraethylammonium application, no significant synaptic potentiation was observed. The tetraethylammonium induced long-term potentiation was also seen to be accompanied by a significant increase in the magnitude of paired-pulse depression measured at interstimulus intervals of 20 and 100 ms, a phenomenon not seen during the expression of tetanically induced long-term potentiation in the dentate gyrus (Christie and Abraham, 1994). Our changes in paired pulse depression were seen to be persistent, lasting as long as recording was continued, unlike the transient change in paired-pulse facilitation reported by Grover (1998) following the induction of a NMDA receptor independent form of long-term potentiation in CA1 pyramidal cells. These findings suggest a strong presynaptic component in the induction/expression of the tetraethylammonium-induced potentiation, possibly due to the involvement of mGlu receptors in both the tetraethylammonium-induced potentiation (Coogan et al., 1999a) and also in paired-pulse depression in the dentate gyrus (O'Leary et al., 1997). Interleukin-1β had no effect on paired-pulse depression under baseline conditions, but was found to block the changes in paired-pulse depression at 100 ms intervals following tetraethylammonium application. The effect on paired pulse depression at 20 ms intervals was partially blocked by pre-treatment of slices with interleukin-1β, although this effect did not reach significance in our experiments. The reason for the incomplete block of the changes in paired pulse depression at 20 ms interstimulus interval by interleukin-1β is unknown. We have however previously reported a differential effect of metabotropic glutamate receptor activation on short and middle latency intervals (see O'Leary et al., 1997), and so there remains the possibility that the changes in paired pulse depression at 20 ms elicited by tetraethylammonium are partly mediated by non-specific mechanisms, which cannot be blocked by interleukin-1β.

We have previously reported an inhibitory effect of interleukin-1β on NMDA receptor function (Coogan and O'Connor, 1997). Since interleukin-1β had no effects on AMPA-receptor function in these experiments a postsynaptic locus of action was suggested. The fact that interleukin-1β did not wholly antagonise the tetraethylammonium-induced increase in paired pulse depression in these experiments also suggests that there is an interleukin-1 resistant component in the tetraethylammonium induced long-term potentiation. However, the results presented here do not provide conclusive evidence for either a pre-synaptic or postsynaptic action of interleukin-1β. Such actions could include the inhibition of retrograde messenger production, such as arachidonic acid, thus in turn preventing changes in transmitter release probability (Lynch and Voss, 1990; Murray et al., 1997).

The finding that the application of interleukin-1β following the establishment of tetraethylammonium induced long-term potentiation had no effect suggests that interleukin-1β inhibits the induction phase of long-term potentiation only. The interleukin-1β induced inhibition of tetraethylammonium induced long-term potentiation was not due to contamination of interleukin-1β by heat-stable endotoxin since heat denatured interleukin-1β had no effect on its own. The reversal of the interleukin-1β induced antagonism of tetraethylammonium induced long-term potentiation by pre-treatment of slices with interleukin-1 receptor antagonist suggests that the interleukin-1β effect is a specific one, probably mediated by interleukin-1β binding to interleukin-1, type 1 receptors (Cremona et al., 1998). This finding is in agreement with the reported antagonism by interleukin-1 receptor antagonist of other interleukin-1β mediated effects in the brain (Plata-Salaman and ffrench-Mullen, 1992, 1994; Miller and Fahey, 1994). It is also interesting to note that interleukin-1 receptor antagonist applied on its own did not affect tetraethylammonium induced long-term potentiation or paired pulse depression. This is in contrast to recent reports which have shown that interleukin-1 receptor antagonist may have an inhibitory effect on tetanically induced long-term potentiation in the CA1 (Schneider et al., 1998).

The intracellular mechanisms of action of interleukin-1β on synaptic transmission and plasticity are obscure. However activation of the p38 MAP kinase cascade, a protein kinase cascade activated in many cell types in response to pro-inflammatory cytokines and cellular stresses (Raingeaud et al., 1995; Kyriakis and Avruch, 1996) and which has a high constitutive expression in the hippocampus (Carletti et al., 1995), seems to be required for the interleukin-1β induced inhibition of long-term potentiation and NMDA receptor mediated transmission (Coogan and O'Connor, 1997). We therefore examined the possibility that the p38 MAP kinase cascade might be involved in the interleukin-1β induced inhibition of tetraethylammonium induced long-term potentiation. The p38 MAP kinase inhibitor, SB203580 (Cuenda et al., 1995), at a concentration previously shown to block interleukin-1β induced effects in the dentate gyrus (Coogan et al., 1999b), was found to inhibit tetraethylammonium induced long-term potentiation. This may suggest that activation of the p38 MAP kinase cascade is required for expression of tetraethylammonium induced long-term potentiation. Since SB203580 itself inhibited the induction of tetraethylammonium induced long-term potentiation, it was not possible to investigate if SB203580 attenuated interleukin-1β's inhibitory effect on tetraethylammonium induced long-term potentiation. Both tetanic- and tetraethylammonium induced long-term potentiation have previously been shown to be inhibited by the p42/44 MAP kinase cascade inhibitor PD98059, in both the CA1 and dentate gyrus (English and Sweatt, 1997; Coogan et al., 1999a). A recent report suggests that activation of the p42/44 MAP kinase by glutamate in striatal neurones is dependent on p38 MAP kinase activity (Vincent et al., 1998). Thus the expression of tetraethylammonium induced long-term

potentiation may require p38 MAP kinase dependent activation of p42/44 MAP kinase cascade.

The differential effect of the p38 MAP kinase cascade on tetanically induced long-term potentiation (activation by interleukin-1β seems to lead to inhibition of long-term potentiation) and tetraethylammonium induced long-term potentiation (activation seems to be required for expression of tetraethylammonium induced long-term potentiation) suggests that the intracellular mechanisms of interleukin-1β action on the two phenomena may be separate and distinct. SB203580 did not inhibit the tetraethylammonium-induced changes in paired-pulse depression, also suggesting a locus of action on tetraethylammonium induced long-term potentiation that is separate and distinct form that of interleukin-1β. What intracellular cascades mediate the effects of interleukin-1β on tetraethylammonium induced long-term potentiation and the tetraethylammonium-induced changes in paired pulse depression remain obscure at present.

It has been hypothesised that in the aged hippocampus long-term potentiation expression is more dependent on voltage-dependent Ca^{2+} channel activation than in the young brain (Shankar et al., 1998). It has also been proposed that impairment of long-term potentiation in aged rats is correlated with increased expression of interleukin-1β in the hippocampus (Murray and Lynch, 1998). It is therefore possible that the inhibition of tetraethylammonium induced long-term potentiation by interleukin-1β may represent a model by which increased interleukin-1β expression in aged brain may serve to inhibit long-term potentiation, and possibly impair new memory formation. It is unclear from the presented data if interleukin-1β serves to inhibit tetraethylammonium induced long-term potentiation via modulation of voltage-dependent Ca^{2+} channels (Plata-Salaman and ffrench-Mullen, 1992, 1994) mGlu receptors or via modulation of biochemical cascades which may underpin the expression of tetraethylammonium induced long-term potentiation. Further physiological and biochemical analysis of the action of both interleukin-1β and tetraethylammonium in the hippocampus would help to resolve these questions.

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