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Cytokine-mediated inflammatory hyperalgesia limited by interleukin-13

Abstract

The effect of interleukin-13 (IL-13) on hyperalgesic responses to intraplantar (i.pl.) injection of carrageenin, E. coli endotoxin (LPS), bradykinin, tumour necrosis factor a (TNF-a), interleukin-1b (IL-1b), interleukin-8 (IL-8) and prostaglandin E2 (PGE2) was investigated in a model of mechanical hyperalgesia in rats. Also, the cellular source of the IL-13 was investigated. IL-13, administered 30 min before the stimulus, inhibited responses to carrageenin, LPS, bradykinin, and TNF-a, but not responses to IL-1b, IL-8 and PGE2. IL-13, administered 2 hours before the injection of IL-1b, did not affect the response to IL-1b, whereas IL-13, administered 12 hours or 12 + 2 hours before the IL-1b, inhibited the hyperalgesia

(– 35%, – 77%, respectively). In murine peritoneal macrophages, IL-13 administered 2 hours before stimulation with LPS, inhibited the production of IL-1b (– 67%) and PGE2 (– 56%). IL-13 administered 12 hours before stimulation with LPS inhibited LPS-stimulated PGE2 but not IL-1b. An anti-IL-13 serum potentiated responses to carrageenin, LPS, bradykinin and TNF-a (but not IL-1b and IL-8), as well as responses to bradykinin in rats depleted of mast cells with compound 40/80, but not in athymic rats. These data suggest that IL-13, released by lymphocytes, limits inflammatory hyperalgesia by the inhibition of the production TNF-a, IL-1b, IL-8 and PGs.

Full text

INTRODUCTION

The sensitisation of pain receptors is the common factor in all types of inflammatory pain. This functional up-regulation of pain receptors leads to a clinical state known as hyperalgesia. Following such sensitisation, previously ineffective stimuli cause "overt pain" in humans, or a characteristic behaviour in laboratory animals that may be used as an end point in nociceptive tests [1]. There are two groups of directly-acting hyperalgesic mediators that satisfy experimental and clinical criteria for directly acting nociceptor sensitisers: arachidonic acid/cyclo-oxygenase products, in particular prostaglandins such as PGE_2, and sympathomimetic amines. The capacity of prostaglandins to sensitise pain receptors has been shown in man and in animals using both behavioural and electrophysiological techniques [2]. Also, the sympathomimetic amines, noradrenaline and dopamine have been shown to functionally up-regulate nociceptors in man and in experimental animals [3-7].

Although the "final" peripheral hyperalgesic mediator may be either a prostaglandin or a sympathomimetic amine, the release of these mediators is secondary to that of bradykinin and a cascade of cytokines. The pro-inflammatory agents, carrageenin and bacterial endotoxin (lipopolysaccharide, LPS) stimulate the release of bradykinin, which stimulates the release of TNF-alpha. The TNF-alpha stimulates the production of IL-1beta and IL-6, which in turn stimulate the production of cyclo-oxygenase products, and IL-8, which stimulates the production of sympathomimetic amines [8-11]. In a different model of inflammatory hyperalgesia, the tail flick method, hyperalgesic responses to LPS and TNF-alpha were IL-1beta-dependent, but PG-independent

[12, 13]. A role for TNF-alpha in pain, in man is suggested by a report that a "humanised" monoclonal antibody to TNF-alpha relieved arthritic pain [14].

In the last decade, cytokines generally regarded as "anti-inflammatory" have been described which inhibit the production of IL-1beta, IL-6, IL-8 and TNF-alpha, cytokines which are generally regarded as "pro-inflammatory". Such distinctions are almost certainly too simplistic, particularly in regard to IL-6, which actually has more pro-inflammatory than anti-inflammatory actions [15]. The class of anti-inflammatory cytokines includes, IL-4, IL-10, IL-13 and TGF-beta [16-22]. IL-4, released by mast cells, and IL-10, probably originating from local macrophages, inhibited the hyperalgesic responses to carrageenin and bradykinin by two mechanisms: inhibition of the production of hyperalgesic cytokines, and inhibition of prostaglandin production [23, 24]. The latter was the result of the suppression of cyclo-oxygenase-2 (COX-2) by IL-10 and IL-4 [25-27].

IL-13, which is produced mainly by Th2 lymphocytes and by mast cells [28-29], shares a number of biological properties with IL-4, including the inhibition of the production of pro-inflammatory cytokines and eicosanoids [17-19, 27, 30, 31]. IL-4 and IL-13 also enhance B-cell proliferation, up-regulate the expression of MHC class II antigens and act as switch factors for induction of IgE production [32-34]. The overlapping biological properties of IL-4 and IL-13 reflects shared receptor elements in their signal transduction systems [17]. In view of the recently described anti-hyperalgesic effects of IL-4 [24], and the capacity of both IL-4 and IL-13 to inhibit the production of pro-inflammatory cytokines, such as TNF-alpha, IL-1beta, and IL-8, we tested the possibility that IL-13 limits inflammatory hyperalgesia by diminishing cytokine-mediated hyperalgesic responses to carrageenin, bradykinin, and pro-inflammatory cytokines. In addition, the source of the IL-13 released in inflammatory hyperalgesia was investigated.

MATERIALS AND METHODS

Animals

Male Wistar or Nude-Rowett (athymic) rats, weighing 130-180 g, housed in temperature controlled rooms (22-25° C) with water and food *ad libitum* until use.

Drugs

The following materials were obtained from the sources indicated. Sheep anti-IL-13 serum and pre-immune serum, recombinant human IL-1beta, IL-8, IL-13, TNF-alpha, murine IL-1beta (National Institute for Biological Standards and Control, NIBSC, cytokine preparations coded 86/680, 89/520, 94/622, 87/650 and 93/668). The specific activities of these materials are IL-1beta: 100,000 international units (iu) 1 mug^{-1} $ampoule^{-1}$, IL-8: 1,000 iu mug^{-1} $ampoule^{-1}$, IL-13: 1,000 iu mug^{-1} $ampoule^{-1}$, TNF-alpha: 40,000 iu 1 mug^{-1} $ampoule^{-1}$, murine IL-1beta 100,000 iu 0.1 mug^{-1} $ampoule^{-1}$). Carrageenin (FMC Corporation, Philadelphia, USA). PGE_2, bradykinin, dextran, concanavalin A (Con-A) compound 48/80 and thioglycollate (Sigma, St. Louis, USA). Bacterial endotoxin from *E. coli* 055:B5 (referred to here as lipopolysaccharide, LPS, Difco Laboratories Ltd, West Molsey, Surrey, UK). PGE_2 assay reagents and ^3H-thymidine (Amersham International plc, UK).

The LPS content of the above materials, as measured in a limulus amoebocyte lysate test, was of the order of 0.25 iu mg^{-1}, which is equivalent to a little over 10^{-15} g of LPS in a hyperalgesic dose of IL-1beta (0.5 pg), for example. The threshold hyperalgesic dose of LPS in the above model is some 100 ng, *i.e.* 10^{-7} g (based upon published data, [8]). Therefore, the doses of the hyperalgesic agents used contained amounts of LPS up to eight log_{10} s less than the threshold hyperalgesic dose of LPS.

Nociceptive test

A constant pressure of 20 mm Hg was applied to the hind-paws of rats and discontinued when they presented a typical freezing reaction (reaction time). This reaction was characterised by a reduction of escape movements: animals usually made several attempts to escape from the position imposed by the experimental situation. These were followed by alterations in respiratory frequency with the onset of a typical shivering reaction. The intensity of hyperalgesia was quantified as the variation in reaction time (delta reaction time) obtained by subtracting values measured 3 hours after administration of hyperalgesic substances from (control) reaction times measured before injection at time zero [35]. Different individuals prepared the solutions to be injected, made the injections, and measured the reaction times. Reaction times were typically 32-34 s (with s.e. means of 0.5-1.0 s) before injection and 2-4 s

after stimulation with hyperalgesic agents. Multiple paw treatments did not alter basal reaction times.

In vivo *measurements*

Hyperalgesia was measured 3 hours after injections (in 100 mul, i.pl.) of carrageenin (10 or 100 mug), LPS (1 mug), bradykinin (50 or 500 ng), TNF-alpha (0.25 or 2.5 pg), IL-1beta (0.05 or 0.5 pg), IL-8 (10 pg or 100 pg), and PGE_2 (10 or 100 ng) into the hind-paws of rats. The larger doses of hyperalgesic agents were the smallest that evoked maximum responses and the time interval of 3 hours was a time at which responses to the chosen doses of hyperalgesic agents were at or close to their peak [8-10, 23, 36]. The order of potency of the cytokines was IL-1beta > TNF-alpha > > IL-8 for these human sequence cytokines in rats [10]. Whether this order of potency reflects the order of potency of the endogenous cytokines of the rat is unknown. The rat sequence cytokines were not available for this study and certain cytokines exhibit species preference or specificity [38-39]: the native cytokines remain to be tested. IL-13 (10 ng in 50 mul, i.pl.) or saline (50 mul) was injected in the (same) hind-paws, 30 min, 2 hours, 12 hours, or 12 hours + 2 hours before hyperalgesic agents. Anti-IL-13 serum (50 mul, i.pl.) was injected into hind-paws 30 min before carrageenin, LPS, bradykinin, TNF-alpha, IL-1beta and IL-8. Anti-IL-13 serum (50 mul, i.pl.) was injected into the hind-paws of athymic rats and, 30 min later, bradykinin (50 ng, 100 mul) was injected into the (same) hind-paws. Hyperalgesia was assessed after a further 3 hours. Also, hyperalgesia was measured 3 hours after injection of bradykinin into hind-paws of rats depleted of mast cells by chronic administration (in 50 mul, i.pl.) of compound 48/80 (day 1: 1 mug, day 2: 3 mug, days 3 and 4: 10 mug). Bradykinin (50 ng, 100 mul, i.pl.) was injected on day 5.

In vitro *measurements*

Murine peritoneal macrophages, harvested from the peritoneal cavities of mice treated, three days earlier, with sterile thioglycollate (2 ml of a 3% w/v solution), were allowed to adhere to 24-well plastic tissue culture plates. The macrophages were seeded at 10^6 cells ml^{-1} $well^{-1}$ in RPMI with 10% foetal calf serum, penicillin (100 U ml^{-1}) and streptomycin (100 $mg.ml^{-1}$), for 1 hour at 37° C, in an atmosphere of 5% CO_2 in air. The monolayers that formed were washed three times with phosphate-buffered saline (PBS), pH 7.4, and cultured at 37° C with the following: (a) RPMI medium, (b) LPS (1 $mug.ml^{-1}$), © IL-13 (1.5 and 15

ng.ml^{-1}), (d) IL-13 (1.5 and 15 ng.ml^{-1}) and, 12 hours later, LPS (1 mug.ml^{-1}), (e) IL-13 (15 ng.ml^{-1}) and, 2 hours later, LPS (1 mug.ml^{-1}). After culture for a further 24 hours, the concentrations of PGE_2 and IL-1beta in the supernatants were measured, using, respectively, a PGE_2 assay kit (Amersham, as described [23]) and a specific ELISA. The protocol for the ELISA was based upon a protocol described previously [40]. Briefly, sheep polyclonal anti-mouse IL-beta IgG, raised against recombinant mouse IL-1beta (2 mug.ml^{-1}) in 100 mul PBS buffer, was used to coat microtiter plates (Nunc Maxisorb). After incubation (4° C overnight), and washing of the plates in assay buffer (0.01 M phosphate, 0.05 M NaCl, 0.1% Tween 20, pH 7.2), 100 mul of standard (recombinant mouse IL-1beta), or sample, was added to each well and incubated overnight at 4° C. After washing the plates, 100 mul of biotinylated, sheep polyclonal anti-mouse IL-beta IgG (diluted 1/1,000 with assay buffer + 1% normal sheep serum), was added to the plates and incubated for 1 hour at room temperature. Subsequent steps were as described previously [40].

Data analysis

Results are presented as means with s.e. means of groups of 5 animals for the *in vivo* measurements and of 3 replicates for the *in vitro* cytokine measurements. Three independent *in vitro* experiments were performed, each giving similar results. The results of formal statistical tests are not reported: a mean value described as different from another mean value, differed by more than three times (and usually five to ten times) the larger s.e. mean.

RESULTS

*Effect of IL-13 on hyperalgesic responses to carrageenin, LPS, bradykinin, TNF-*alpha*, IL-1*beta*, IL-8 and PGE_2*

Injection (in 100 mul, i.pl.) of carrageenin (100 mug), bradykinin (500 ng), LPS (1 mug), TNF-alpha (2.5 pg), IL-1beta (0.5 pg), IL-8 (100 pg) and PGE_2 (100 ng) into the hind-paws of Wistar rats evoked hyperalgesia, measured 3 hours after injections. Treatment with IL-13 (2.5-10 ng, 50 mul, i.pl.), 30 min before carrageenin, bradykinin, or TNF-alpha inhibited, in a dose-dependent manner, hyperalgesic responses to these agents. IL-13 (10 ng, i.pl.) inhibited the hyperalgesic responses to carrageenin, LPS, bradykinin and TNF-alpha by 88, 71, 80 and 82%, respectively. Hyperalgesic responses to IL-1beta, IL-8 and PGE_2

were not affected by IL-13 (Figure 1). Although IL-13 (10 ng, i.pl.) injected 2 hours before IL-1beta (0.5 pg, i.pl.), did not affect the response to IL-1beta, when IL-13 was given 12 hours or 12 hours + 2 hours before IL-1beta, the hyperalgesic response to this cytokine was inhibited by 35 and 77%, respectively (Figure 2A). The hyperalgesic response to IL-8 (100 pg, i.pl.) was not inhibited by IL-13 (10 ng, i.pl.) injected during any of the three schedules (2 hours, 12 hours and 12 hours + 2 hours before IL-8, Figure 2B). There was no visible paw inflammation following treatment with IL-13.

*Effect of IL-13 on the production of IL-1*beta *and PGE_2 by murine peritoneal macrophages stimulated with LPS*

Murine peritoneal macrophages stimulated with LPS (1 mug.ml^{-1} for 16 hours) produced IL-1beta, and this production was not inhibited by addition to the macrophages of IL-13 (1.5 or 15 ng.ml^{-1}) 12 hours before stimulation with LPS. Addition to the macrophages of IL-13 (15 ng.ml^{-1}), 2 hours before stimulation with LPS, inhibited the production of IL-1beta (- 67%, Figure 3A). Stimulation of the macrophages with LPS (1 mug.ml^{-1}) also evoked release of PGE_2, and this release was inhibited, by 22 and 85%, by the treatment of the macrophages for 12 hours with IL-13 at 1.5 and 15 ng.ml^{-1}, respectively. Treatment of macrophages with IL-13 (15 ng.ml^{-1}) 2 hours prior to stimulation with LPS (1 mug.ml^{-1}) also inhibited LPS-induced release of PGE_2 (- 56%, Figure 3B).

*Potentiation by a sheep anti-IL-13 serum of hyperalgesic responses to carrageenin, LPS, bradykinin, TNF-*alpha*, but not IL-1*beta *and IL-8*

A sheep anti-13 serum (50 mul, i.pl.), but not a pre-immune (control) serum (50 mul, i.pl.), injected 30 min before injections (i.pl.) of carrageenin (10 mug), bradykinin (50 ng) and TNF-alpha (0.25 pg) potentiated responses, measured 3 hours after injection, of these hyperalgesic agents (carrageenin = + 64%, LPS = + 111%, bradykinin = + 112%, TNF-alpha = + 114%). Hyperalgesic responses to IL-1beta (0.05 pg, i.pl.) and IL-8 (10 pg, i.pl.) were not affected by the sheep anti-IL-13 serum (Figure 4).

Failure of a sheep anti-IL-13 serum to potentiate the hyperalgesic response to bradykinin in athymic (nude) rats

In athymic Nude-Rowett rats, a sheep anti-13 serum (50 mul, i.pl.), injected 30 min before injection of bradykinin (50 ng, i.pl.), failed to potentiate the hyperalgesic response measured 3 hours after injection of bradykinin (Figure 5A). The absence of the thymus in the Nude-Rowett rats was confirmed by histopathological analysis, and in a splenocyte proliferation assay using Con-A. Proliferative responses (^{3}H-thymidine incorporation, cpm) to Con-A (5 mug.ml^{-1}) were for Wistar rats, culture medium alone = 1,320 ± 140 cpm, Con-A = 12,316 ± 940 cpm and for Nude-Rowett rats, culture medium alone = 1,050 ± 128 cpm, Con-A = 970 ± 90 cpm. In contrast, in naive wild type Wistar rats and wild-type Wistar rats depleted of mast cells (by local treatment, i.pl., with compound 48/80), a sheep anti-13 serum (50 mul, i.pl.) potentiated by 112 and 62% respectively, responses to bradykinin (50 ng, i.pl.), measured 3 hours after its injection. The depletion of mast cells in the paws was confirmed by histopathological analysis.

DISCUSSION

Interleukin-13 belongs to a class of cytokines with anti-inflammatory activity. The other cytokines in this class are IL-4, IL-10 and TGF-beta. The anti-inflammatory activity of these cytokines is a consequence of their capacity to inhibit the production and action of inflammatory cytokines, such as TNF-alpha, IL-1beta, IL-6 and chemokines [16-22, 30, 31]. The anti-inflammatory cytokines also inhibit the induction of the enzymes COX-2 and NOS-2, which are involved in the production of (the inflammatory mediators) PGs and NO, respectively [18, 25, 27, 41-44]. In the present study, a model of inflammatory hyperalgesia (a rat paw pressure test) was used to assess whether or not IL-13 was able to exert an anti-hyperalgesic effect. In this test, carrageenin and LPS caused hyperalgesia by stimulating the release of bradykinin, which initiated a cascade of cytokine release [8, 10, 11].

Local injection of IL-13 inhibited, in a dose-dependent manner, hyperalgesic responses to the inflammatory stimuli carrageenin and LPS, and responses to the endogenous hyperalgesic mediators, bradykinin and TNF-alpha, which are induced by carrageenin and LPS. These anti-hyperalgesic effects of IL-13 are likely to have involved the inhibitory effect of IL-13 on the production of TNF-alpha, IL-1 and IL-8 [30, 31], since in carrageenin-evoked and LPS-evoked hyperalgesia, bradykinin is produced and triggers the release of TNF-alpha which, in turn, stimulates the release of IL-1 and IL-8 [8]. Consistent with this

hypothesis, the release of IL-1 by LPS-stimulated murine peritoneal macrophages was inhibited by their treatment with IL-13. In contrast, IL-13 injected locally, 30 min before IL-8 or PGE_2, did not inhibit the hyperalgesic responses to these mediators. The absence of an effect of IL-13 on hyperalgesic responses to IL-8 and PGE_2 was predicted because the mode of action of these mediators does not require cytokine production. IL-8 evokes local production of sympathetic amines, which along with PGE_2, sensitise nociceptors [9, 36]. Even when administered 2, 12 or 12 + 2 hours before IL-8, IL-13 failed to inhibit IL-8-induced hyperalgesia. These results for IL-13 are similar to those obtained with IL-10 and IL-4, which also have the capacity to inhibit the production of hyperalgesic cytokines [23, 24].

In contrast to IL-10 [23], but in common with IL-4 [24], IL-13 injected 30 min or 2 hours before IL-1beta did not inhibit its hyperalgesic effect. Inhibition was observed only when IL-13 was injected either once, 12 hours before, or twice, at 12 hours + 2 hours before the administration of IL-1beta. Since IL-1beta-induced hyperalgesia is mediated by eicosanoid products [36, 45], the effect of IL-13 on PGE_2 production by activated macrophages was investigated. Like IL-4 [24], IL-13 inhibited, in a dose-dependent manner, PGE_2 production when the macrophages were pre-treated with IL-13 for 12 hours but, in contrast to IL-4, IL-13 also inhibited PGE_2 production when the macrophages were pre-treated with IL-13 for just 2 hours. These results are consistent with IL-1beta evoking hyperalgesia *via* the release of PGs [36, 45]. The finding that administration of IL-13 into the paws of rats 2 hours before IL-1beta did not inhibit the evoked hyperalgesia does not concur with the inhibition by IL-13 of PGE_2 production *in vitro* (by LPS-stimulated murine peritoneal macrophages). There are a number of possible explanations for this difference: (i) a species difference, (ii) a greater sensitivity to inhibition by IL-13 of LPS-evoked PGE_2 production by peritoneal macrophages than IL-1beta-evoked PGE_2 production by macrophages in the paw, and (iii) a reduction by IL-13 in IL-1beta-evoked PGE_2 production in the paw leaving sufficient PGE_2 production to mediate hyperalgesia. The partial inhibition of PGE_2 production following the treatment for 2 hours of murine peritoneal macrophages with IL-13, concurs with data showing that the release of PGE_2 by human synovial fibroblasts stimulated with IL-1beta is only partially inhibited by IL-13 [26]. The effect of IL-13 on IL-1beta-induced hyperalgesia reported here is similar to the effect of IL-4 in the same model [24]. Although IL-13 inhibits the induction of iNOS [46], the anti-hyperalgesic effect of IL-13 is not a consequence of a reduction in the production of NO because, in the model of

mechanical hyperalgesia used in the present study, NO has an anti-hyperalgesic effect, rather than a hyperalgesic effect [47, 48]. In contrast, a hyperalgesic effect of NO has been reported in other models of hyperalgesia, such as the tail-flick and hot-plate tests, acetic acid- or phenyl-p-quinone-induced writhing and formalin-induced paw licking in mice [49-54]. The simplest explanation for these conflicting observations is that the role and (relative) importance of this pathway varies among the groups of primary sensory neurones stimulated by different types of nociceptive stimuli.

Antibodies neutralising rat IL-10 and IL-4 were used in experiments that showed that endogenous IL-10 and IL-4 have a role in limiting the development of inflammatory hyperalgesia triggered by carrageenin, bradykinin and TNF-alpha [23, 24]. Here we show that the hyperalgesic responses to carrageenin, LPS, bradykinin and TNF-alpha were enhanced by treatment with an antiserum neutralising IL-13. These data suggest that, like IL-10 and IL-4, endogenous IL-13 limits inflammatory hyperalgesia. The finding that the anti-IL-13 serum did not enhance hyperalgesic responses to IL-1beta and IL-8 suggests that the main effect of endogenous IL-13 on inflammatory hyperalgesia is the inhibition of release of cytokines rather than inhibition of the production of "downstream" mediators (PGs and sympathetic mediators) that sensitise nociceptors [7, 35]. The endogenous IL-13 that limited the inflammatory hyperalgesia was probably released locally because the injection of anti-IL-13 serum into the ipsi-lateral paw did not enhance responses to hyperalgesic stimuli injected into the contra-lateral paw (data not shown).

IL-13 and IL-4 are released mainly by Th2 lymphocytes and by mast cells [28, 29, 55, 56]. The endogenous IL-4 that limits inflammatory hyperalgesic responses to carrageenin is released mainly by mast cells [24]. To investigate which cell-type (mast cell or lymphocyte) releases IL-13 during inflammatory hyperalgesia, we investigated the effect of the antiserum to IL-13 on hyperalgesic responses to bradykinin in athymic rats (deficient in T lymphocytes) and in rats depleted of mast cells (with compound 48/80 [57]). Histopathological analysis confirmed the absence of the thymus (in the athymic animals) and the effectiveness of the depletion of mast cells after compound 48/80. The absence of the thymus was also confirmed using a splenocyte proliferation assay. The finding that the anti-IL-13 serum potentiated the hyperalgesic effect of bradykinin in rats depleted of mast cells, but not in athymic rats strongly suggests that T lymphocytes were the source of the IL-13 that limited the inflammatory hyperalgesia. The finding

that an anti-IL-4 antibody potentiated the hyperalgesic response to bradykinin in the athymic animals argues against the possibility that these animals reacted differently from Wistar rats with respect to the development of hyperalgesia.

CONCLUSION

In conclusion, the data described above provide evidence that IL-13, released by lymphocytes, limits the intensity and duration of inflammatory hyperalgesia. Consequently, a lack of IL-13 may contribute to the maintenance of chronic inflammatory pain. IL-13 appears to largely achieve its effects by inhibiting the production of hyperalgesic cytokines (*e.g.* TNF-alpha and IL-1), rather than its effect on COX-2.

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Figures

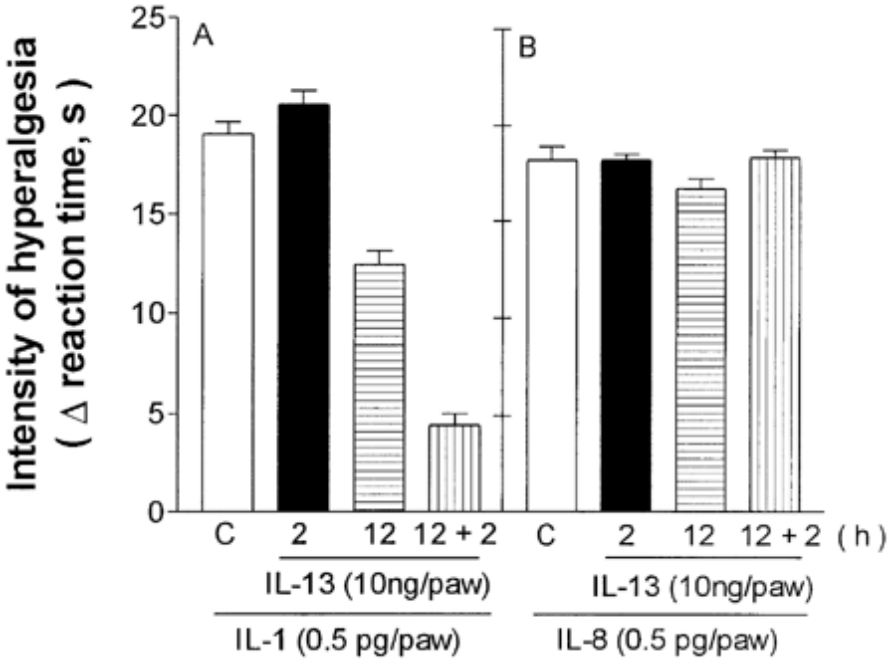


Figure 1

Effect of IL-13 (2.5-10 ng, 100 mul, i.pl.) on the hyperalgesic response to injections (in 100 mul, i.pl.) of carrageenin (Cg, 100 mug), bradykinin (BK, 500 ng),

TNF-alpha (2.5 pg), LPS (1 mug), IL-1beta (0.5 pg), IL-8 (100 pg), and PGE_2, (100 ng).

IL-13 (or saline) was injected into paws, 30 min before the paws were injected with a hyperalgesic agent. The intensity of hyperalgesia was measured 3 hours after injection of the hyperalgesic agents. Means ± s.e. means in groups of 5 rats are shown.

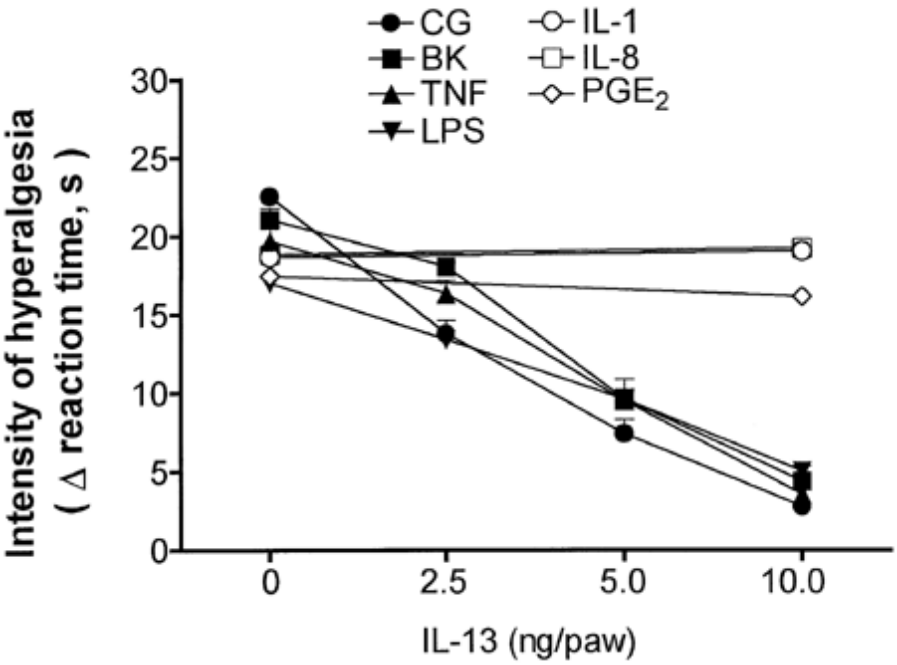


Figure 2

Effect of IL-13 (10 ng, 100 mul, i.pl.) on the hyperalgesic responses to injections (in 100 mul, i.pl.) of IL-1beta (IL-1, 0.5 pg, panel A) and IL-8 (100 pg, panel B).

IL-13 was injected into paws 2 hours, 12 hours, or 2 hours + 12 hours before the hyperalgesic agent was injected. The intensity of hyperalgesia was measured 3 hours after injection of the hyperalgesic agents. Means ± s.e. means for groups of 5 rats are shown.

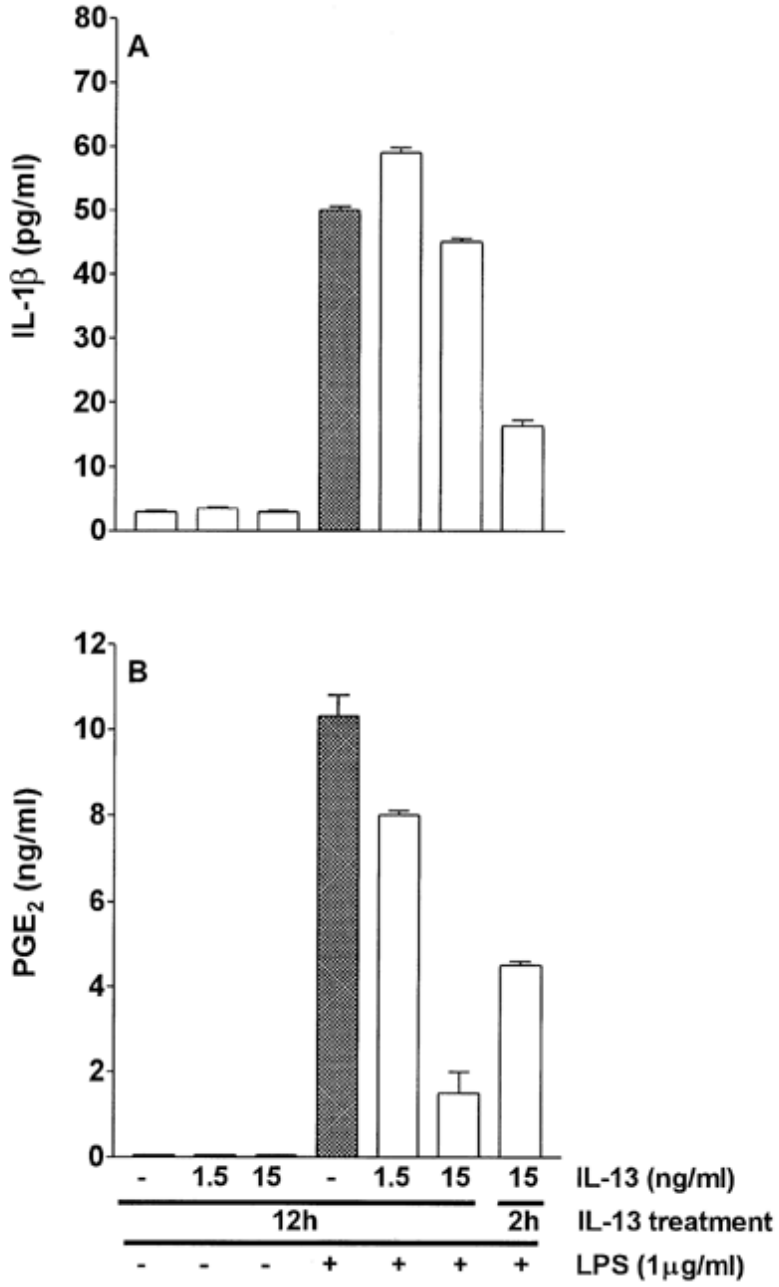


Figure 3

Effect of IL-13 on the production of IL-1beta and PGE by murine peritoneal macrophages stimulated with LPS.

The macrophages (10^6 cells $well^{-1}$) were cultured with IL-13 (1.5 or 15 $ng.ml^{-1}$) in medium (+) or medium alone (-). Two hours or 12 hours later the macrophages were stimulated with LPS (1 $mug.ml^{-1}$) in medium (+) or with medium alone (-) for a further 24 hours. At the end of this period the concentrations of IL-1beta (panel A) and PGE_2

(panel B) in the macrophage-conditioned media were measured. Means ± s.e. means of triplicate wells are shown.

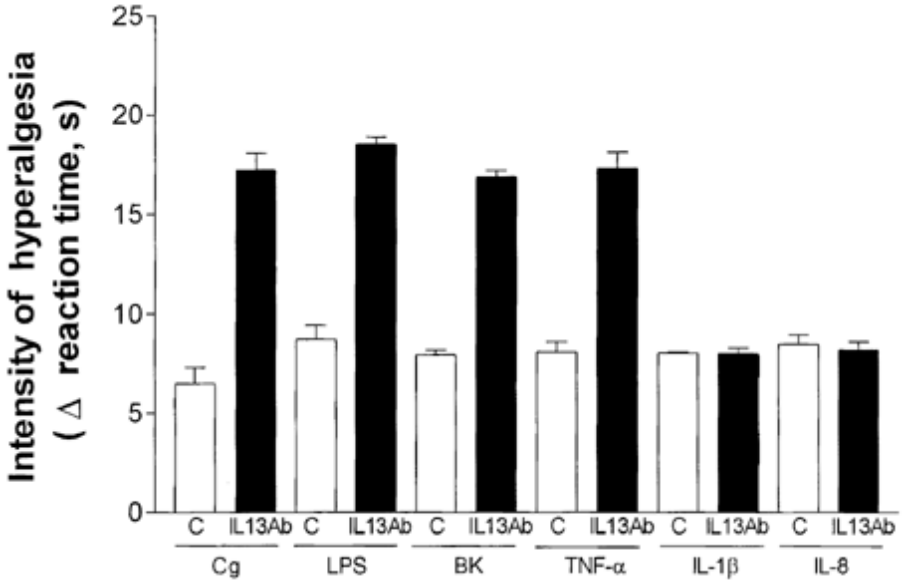


Figure 4

Effect of pre-immune serum (C) and sheep anti-IL-13 serum (IL-13Ab, 50 mul, i.pl.), on hyperalgesic responses to injections (in 100 mul, i.pl.) of carrageenin (Cg, 10 mug), bradykinin (BK, 50 ng), LPS (0.1 mug), TNF-alpha (0.25 pg), IL-1beta (0.05 pg), and IL-8 (10 pg).

One of the sera was injected into paws, 30 min before the hyperalgesic agent was injected. The intensity of hyperalgesia was measured 3 hours after injection of the hyperalgesic agents.

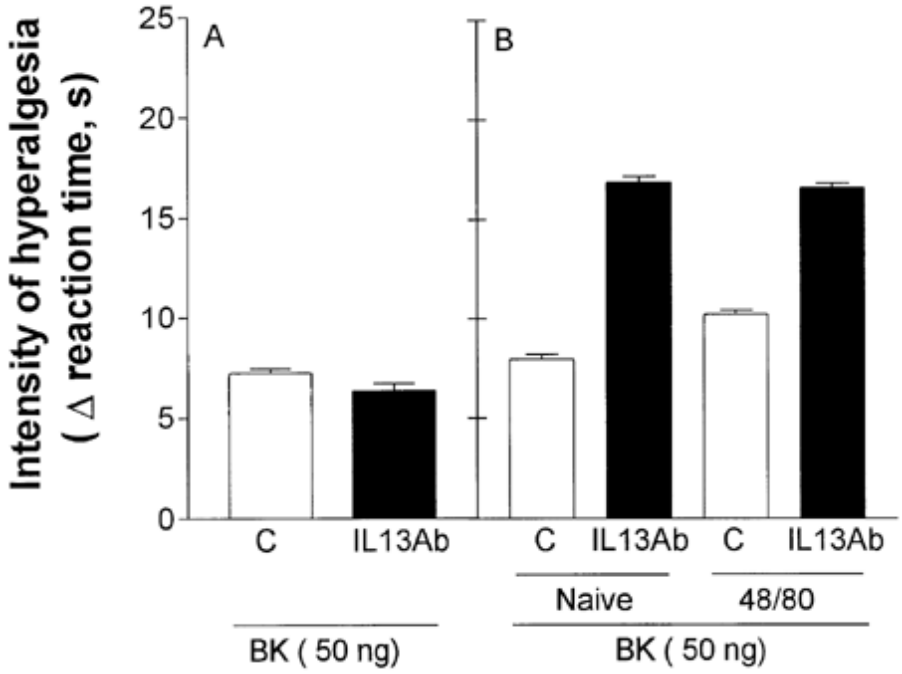


Figure 5

Effect of pre-immune serum (C) and sheep anti-IL-13 serum (IL-13Ab, 50 mul, i.pl.), on hyperalgesic responses to bradykinin (BK, 50 ng, 100 mul, i.pl.) in athymic (Nude-Rowett) rats (panel A), wild type rats (panel B, left-hand columns) and wild type rats depleted of mast cells (panel B, right-hand columns).

The sera were injected into paws, 30 min before the bradykinin was injected. The intensity of hyperalgesia was measured 3 hours after injection of the hyperalgesic agents. Means ± s.e. means in groups of 5 rats are shown.

Authors

B.B. Lorenzetti, S. Poole, F.H. Veiga, F.Q. Cunha, S.H. Ferreira

Division of Endocrinology, National Institute for Biological, Standards and Control, Blanche Lane, South Mimms, Potters Bar, Herts EN6 3QG, United Kingdom.

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