Interleukin 1 Suppresses Inflammation in Rabbit Colitis

Mediation by Endogenous Prostaglandins

Fabio Cominelli, Cynthia C. Nast, Rafael Llerena, Charles A. Dinarello, and Robert D. Zipser
Departments of Medicine and Pathology and Inflammatory Bowel Disease Center, Harbor-University of California Los Angeles Medical Center, Torrance, California 90502; and Department of Medicine, Tufts University, Boston, Massachusetts 02111

Abstract

Pretreatment with low-dose IL-1 has protective effects in animal models of inflammation or tissue injury, but the mechanisms of these protective effects are not established. To determine if prostaglandins are involved, we administered human recombinant IL-1β and measured rectal PGE_2 production in rabbits with formalin-immune complex colitis. IL-1β (0.3 μg/kg) administered 24 h before induction of colitis increased PGE_2 (231±36 to 1,299±572 pg/ml, $P < 0.01$) and reduced subsequent inflammatory cell infiltration index (from 2.8±0.3 to 1.4±0.3, $P < 0.02$) and edema (from 2.5±0.3 to 1.3±0.3, $P < 0.01$) compared with vehicle-matched animals. Administration of ibuprofen (10 mg/kg i.v.) together with IL-1β prevented the stimulation of PGE_2 and the reduction in inflammation. Colonic PGE_2 production correlated inversely with subsequent severity of inflammation ($P < 0.02$, $r = -0.39$) and edema ($P < 0.04$, $r = -0.35$). IL-1-administration 30 min before induction of colitis did not affect the severity of inflammation. Similarly, pretreatment with a noninflammatory synthetic peptide (fragment 163–171) of human IL-1β, either 30 min or 24 h before colitis induction, did not reduce inflammation or increase prostaglandin synthesis. These data demonstrate that pretreatment with IL-1β 24 h before the induction of colitis reduces inflammation by a mechanism that requires prostaglandin synthesis. (*J. Clin. Invest.* 1990. 85:582–586.) interleukin 1 • prostaglandin E_2 • colitis

Introduction

The systemic infusion of IL-1 in rabbits induces several hemodynamic and metabolic changes typical of severe inflammatory reactions, including fever, neutrophilia, synthesis of hepatic acute phase proteins, hypotension, and increased corticosteroid production (1–4). In contrast, pretreatment with a single low-dose of recombinant IL-1β protects against subsequent inflammation and tissue injury in animal models of gram-negative infection (5), damage from alkylating agents and radiation (6, 7), contact hypersensitivity (8), and arthritis (9). The mechanisms of these protective effects of IL-1 pretreatment are not established and may involve different actions of IL-1 in the various models. A role for IL-1–stimulated prostaglandin production has been suggested in the cutaneous hypersensitivity model, because indomethacin abrogates the protective effects of IL-1, and exogenous prostaglandins produce protection similar to IL-1 (8).

We have recently demonstrated that infusions of IL-1α and IL-1β into perfused rabbit colon and incubations of IL-1 with colon tissue induce enhanced prostaglandin production (10). There is increasing evidence that prostaglandins have protective effects in chemical, infectious, and immunological damage of colon mucosa (11–14). Our studies have also shown that pretreatment of rabbits with the prostaglandin analogues, 16,16-dimethyl-PGE_2 percutaneously or misoprostol by enema, markedly reduces the subsequent severity of colon inflammation in the formalin-immune complex model (15, 16). Therefore, we hypothesized that pretreatment with low-dose IL-1β would enhance prostaglandin production and reduce inflammatory damage in the rabbit model of formalin-immune complex colitis (17). This model provides a system to test the theory. Local prostaglandin production can be measured by validated rectal dialysis techniques, and inflammation may be quantitated by established histologic criteria (18).

Methods

IL-1 preparations. Human recombinant IL-1β prepared by recombinant DNA technology in *Escherichia coli* was provided by Dr. Steven Gillis (Immunex Corp., Seattle, WA) (19). This preparation has a specific activity of 10^{10} U/mg based upon the D10S (subclone of the D10.G4 T cells) assay (20). The synthetic nonapeptide fragment of human IL-1β (VQGEESNDK, fragment 163–171) as the HCl salt was provided by Dr. Diana Boraschi and Dr. Aldo Tagliabue (Sclavo Research Center, Siena, Italy) (21, 22). The nonapeptide solution was adjusted to pH 7.4 with 0.1 N NaOH. This nonapeptide has similar activity as intact IL-1β in the thymocyte proliferation assay (23). Either IL-1 or the nonapeptide were administered as single intravenous injections in 0.5 ml of pyrogen-free saline. Control rabbits received only the saline vehicle.

Rabbit model of colitis. Colon inflammation was induced in the distal colon of male New Zealand rabbits (2.2–2.5 kg) using a modification of the formalin-immune complex method of Hogdson et al. (17), as is well established in our laboratory (18, 24–26). In brief, rabbits are anesthetized with 2.4 mg/kg xylazine (Mobay Co., Shawnee, KS) and 24 mg/kg ketamine HCl (Aveco Co., Fort Dodge, IA) intramusculary and 4 ml of dilute formalin (0.45%) is administered via a catheter inserted 10 cm into the distal colon. 2 h later, albumin–antialbumin immune complexes in antigen excess are injected intravenously. Over the next 48–72 h, the distal colon develops acute inflammation, characterized by infiltration of neutrophils primarily into the mucosa and submucosa, mucus depletion, crypt abscesses, edema, and scattered areas of necrosis (18). To minimize the variability in the

This work was presented in part at the Western Section of the American Federation of Clinical Research, Carmel, CA, February, 1989, and at the American Gastroenterological Association, Washington DC, May, 1989.

Address reprint requests to Dr. F. Cominelli, Division of Gastroenterology, C-1 Trailer, Harbor-UCLA Medical Center, 1124 W. Carson Street, Torrance, CA 90502.

Received for publication 2 June 1989 and in revised form 29 August 1989.

J. Clin. Invest.

0021-9738/90/02/0582/05 $2.00
Volume 85, February 1990, 582–586

severity of inflammation, colitis was induced simultaneously in a minimum of six experimental and six control animals on each study day. IL-1β or vehicle were administered intravenously either 24 h or 30 min before the formalin enema. Rectal dialysis was performed for 2 h immediately before formalin enema for PGE_2 measurement as previously described (18).

Quantitation of inflammation. Animals were killed 48 h after induction of colitis, and the distal colon removed, coded, and processed for routine light microscopy. All samples were examined in a blind fashion by a single pathologist (Dr. C. C. Nast). Two representative longitudinal sections from each colon were examined as previously described (18). A minimum of eight high-power fields of the mucosa and submucosa from each specimen were separately evaluated for acute inflammatory cells infiltrates (neutrophils and eosinophils). A semiquantitative score of leukocytes per high-power field (l/hpf)[1] was determined for each area examined using the following quantitations: 0 = 0 or 1 l/hpf; 0.5+ = 2–9 l/hpf; 1+ = 10–20 l/hpf; 1.5+ = 21–30 l/hpf; 2+ = 31–40 l/hpf; 2.5+ = 41–50 l/hpf; 3+ = 51–65 l/hpf; 3.5+ = 66–80 l/hpf; 4+ = ≥ 81 l/hpf. The inflammatory index was considered the sum of the averaged mucosal and submucosal scores. Edema was graded on a scale of 0–4+.

PGE_2 radioimmunoassay. PGE_2 was measured in rectal dialysates by validated radioimmunoassay after lipid extraction and purification by Sephadex LH-20 chromatography (24).

Statistical analysis. Results are expressed as mean±SEM. Statistical analysis was performed using a statistical software (BMDP Inc., Los Angeles, CA). Statistical comparisons were performed using the Wilcoxon rank sum test. Correlations were evaluated using the Pearson's r test. The differences were considered significant when the P value was < 0.05.

Results

Effect of IL-1β pretreatment on severity of inflammation. Human recombinant IL-1β (0.3 μg/kg) administered 30 min before induction of colitis did not influence the subsequent severity of colonic inflammation compared with that of placebo-treated colitis animals (Table I). In contrast, IL-1β administered 24 h before colitis induction markedly reduced inflammatory cell index and edema (Table I). A separate group of eight animals, treated with IL-1β 24 h before induction of colitis, additionally received the cyclooxygenase inhibitor ibuprofen (10 mg/kg diluted in sterile saline intravenously; Sigma Chemical Co., St. Louis, MO), 10 min before the IL-1β infusion. The severity of colonic inflammation in this group was similar to the inflammation in the placebo-treated colitis animals and significantly greater than inflammation in the group that received only IL-1 24 h before colitis induction (Table I). Representative histologic sections from each experimental group are shown in Fig. 1.

Additional studies examined the effect of ibuprofen (10 mg/kg i.v.) administered 24 h before induction of colitis. Compared with eight matched placebo-treated colitis animals, ibuprofen had no detectable effect on inflammatory cell infiltration index (3.5±0.4 vs. 3.2±0.3) or edema (2.9±0.3 vs. 2.6±0.3).

Effect of 163–171 peptide pretreatment on severity of inflammation. The nonapeptide was administered in doses of 30 and 300 μg/kg. There were no significant effects of the nonapeptide, administered either 30 min or 24 h before induction of colitis, on inflammatory cell index or edema compared with simultaneous placebo controls (Table II).

Table I. Effect of Pretreatment with IL-1β or Placebo on Severity of Inflammation in Rabbits with Formalin-immune Complex Colitis

	Inflammatory index	Edema
Vehicle 24 h (n = 16)	2.8±0.3	2.5±0.3
IL-1β 0.5 h (n = 8)	2.5±0.5	1.9±0.4
IL-1β 24 h (n = 8)	1.4±0.3*	1.3±0.3‡
IL-1β 24 h + ibuprofen (n = 8)	3.5±0.9	2.9±0.5

IL-1β (0.3 μg/kg) or vehicle (0.5 ml sterile saline) were administered as a single intravenous injection either 0.5 or 24 h before induction of colitis. Colons were assessed histologically 48 h after colitis induction for number of inflammatory cells (0 to 8+) and edema (0 to 4+). Data are the mean±SEM. Statistical analysis was performed using the Wilcoxon rank sum test.
* $P < 0.02$ vs. vehicle.
‡ $P < 0.01$ vs. vehicle.

Effect of IL-1 preparations on colonic PGE_2 production. Data of colonic PGE_2 production measured by rectal dialysis in the 2-h period immediately before induction of colitis are shown in Fig. 2. IL-1β given 30 min before induction of colitis did not alter PGE_2 (315±124 pg/ml) compared with vehicle-treated animals (231±36). In contrast, IL-1β given 24 h before colitis significantly increased PGE_2 (1,229±572, $P < 0.01$) compared with vehicle. Ibuprofen together with IL-1 abolished the increase in PGE_2 production associated with 24-h IL-1 pretreatment (244±174). There appeared to be an inverse relationship between PGE_2 production measured before induction of colitis and the subsequent severity of inflammatory cell index ($P < 0.02$, $r = -0.39$) and edema ($P < 0.04$, $r = -0.35$), suggesting that endogenous prostaglandin stimulation may have protective activity. The nonapeptide fragment of IL-1β, administered in either dose at 30 min or 24 h before induction of colitis, did not alter PGE_2 production compared with vehicle (Fig. 2).

Discussion

These studies demonstrate that pretreatment with a relatively low dose of human recombinant IL-1β 24 h before initiation of colitis markedly diminishes the severity of inflammation measured 48 h after colitis induction in the rabbit model of formalin-immune complex colitis. Pretreatment 30 min before initiation of colitis does not have protective effects. Thus, the protective effect appears to be time dependent in relation to the immune stimuli. Similarly, IL-1 induction of enhanced prostaglandin production in the isolated perfused rabbit colon is also time dependent, requiring several hours of IL-1 infusion to obtain maximum effect (10). In the current study, increased in vivo production of prostaglandins was documented ~ 24 h, but not within 30 min, after IL-1 administration. These data are consistent with the concept that, in some animal models, IL-1 protection may require induction of a secondary mediator, possibly synthesis of prostaglandin-generating enzymes (27). Generation of a secondary mediator, such as prostaglandins, has also been proposed as the mechanism by which sub-

1. *Abbreviation used in this paper:* l/hpf, leukocytes per high-power field.

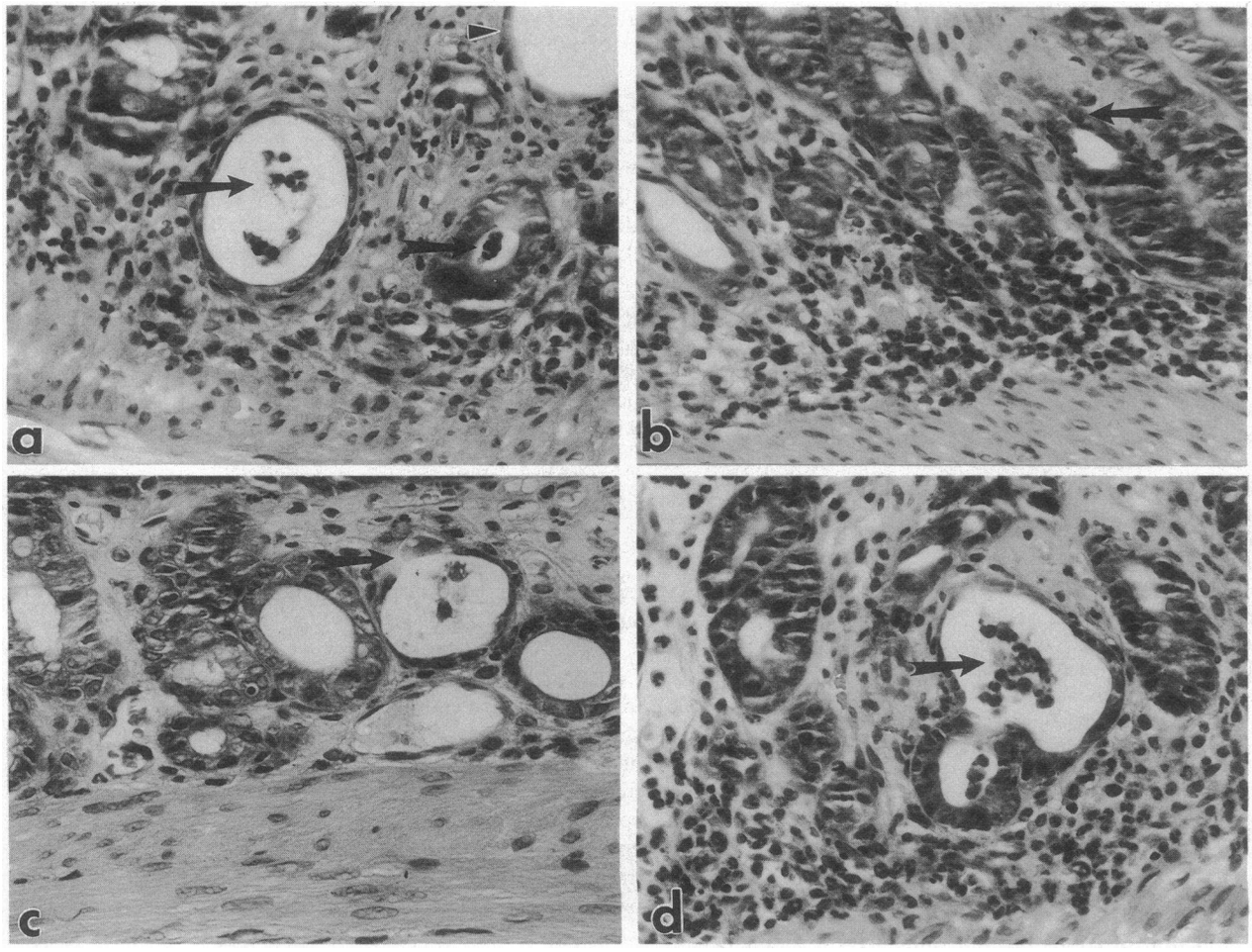

Figure 1. Representative colon histologic appearance 48 h after induction of colitis. (*a*) Placebo. There are neutrophils within the lamina propria, epithelial cell degeneration (*arrowhead*), and crypt abscess formation (*arrows*). (*b*) IL-1β 0.5-h pretreatment. Acute inflammatory cells are throughout the lamina propria and within gland walls (*arrow*). (*c*) IL-1β 24-h pretreatment. There are few neutrophils and focal epithelial cell injury (*arrow*). (*d*) IL-1β 24-h pretreatment with ibuprofen. A marked inflammatory infiltrate is throughout the mucosa with crypt abscess formation (*arrow*). Hematoxylin and eosin ×300.

lethal doses of IL-1 protect against subsequent administration of lethal doses in the mouse (28).

Pretreatment with the cyclooxygenase inhibitor ibuprofen prevented the IL-1 stimulation of prostaglandin synthesis and abrogated the protective effect of IL-1. Our earlier studies demonstrated that pretreatment of animals with either parenteral 16,16-dimethyl-PGE_2 or local misoprostol, a PGE_1 analogue, was also protective in the colitis model (15, 16). In the model of contact hypersensitivity, indomethacin pretreatment similarly prevented the protective effects of IL-1, and prostaglandin administration mimicked IL-1 protective effects (8). Thus, the protective effects of IL-1 pretreatment may involve stimulation of increased prostaglandin synthesis in these models.

Colon prostaglandin production was increased 24 h after IL-1 injection, immediately before induction of colitis. This preinduction of PGE_2 correlated inversely with the subsequent severity of colon inflammation, supporting the concept that PGE_2 protects against development of inflammation. In contrast, PGE_2 production measured 48 h after induction of colitis correlates positively with the severity of inflammation (18). Administration of 16,16-dimethyl-PGE_2 or misoprostol after induction of colitis is ineffective in reducing inflammation (unpublished observations). Thus, protection requires enhanced amounts of prostaglandins before the noxious or immune stimuli. The mechanism of prostaglandin protection is not established and may involve inhibition of leukotriene production (29), inhibition of cytokine production by increasing intracellular cyclic adenosine monophosphate (30), or suppression of immune response including inhibition of mitogen responsiveness, clonal proliferation, and antigenic stimulation (31, 32).

The 163–171 peptide fragment of human IL-1β has immunomodulatory actions similar to complete IL-1β, including T cell activation with enhanced antibody response (22). Pretreatment with this nonapeptide is also radioprotective and restores immune reactivities after sublethal irradiation (23). The HCl salt (the preparation used in our studies) is equipotent to intact IL-1 in each of these actions. In contrast, the 163–171 fragment lacks several of the acute-phase and inflammation-related effects of IL-1, including lack of pyrogenic effects, decreases in plasma iron and glucose, and increases in insulin, corticosteroids, and fibrinogen (21, 22). In addition, the nonapeptide fragment fails to stimulate prostaglandins

Table II. Effect of Pretreatment with the 163–171 Peptide of Human IL-1β or Placebo on Severity of Inflammation in Rabbits with Formalin-immune Complex Colitis

	Inflammatory index	Edema
Vehicle 24 h (n = 8)	3.1±0.4	2.6±0.3
Nonapeptide 0.5 h 30 μg/kg; (n = 8)	2.4±0.3	1.8±0.4
Nonapeptide 24 h 30 μg/kg; (n = 8)	3.1±0.3	2.4±0.3
Vehicle 24 h (n = 8)	3.6±0.6	2.3±0.3
Nonapeptide 0.5 h 300 μg/kg; (n = 8)	3.5±0.5	3.4±0.4
Nonapeptide 24 h 300 μg/kg; (n = 8)	3.1±0.4	3.1±0.4

The 163–171 peptide or vehicle (0.5 ml sterile saline) were administered as a single intravenous injection either 0.5 or 24 h before induction of colitis. Colons were assessed histologically 48 h after colitis induction for number of inflammatory cells (0 to 8+) and edema (0 to 4+). Data are the mean±SEM. Statistical analysis was performed using the Wilcoxon sum rank test. There were no statistical differences between the groups.

from dermal fibroblasts (21). Thus, the nonapeptide was administered in our study to determine if it would display protective effects without stimulating prostaglandin synthesis. However our study demonstrates that the 163–171 fragment of human IL-1β, in doses 100- and 1,000-fold greater than IL-1, does not have protective effects or stimulate prostaglandins in this model.

Enhanced prostaglandin production may not be the protective mechanism in other animal models. Administration of IL-1 several hours before the noxious stimuli is not necessary for protection in some models of injury, including oxygen-induced lung injury (33) and antigen-induced arthritis (9). Furthermore, ibuprofen does not prevent IL-1 protection from gram-negative bacterial infection (5).

Taken together, our data suggest that pretreatment with IL-1 reduces the severity of inflammation in the formalin-immune complex colitis by enhancing production of colon prostaglandins. The protective effect is time dependent, possibly involving the induction of new prostaglandin-synthesizing enzymes.

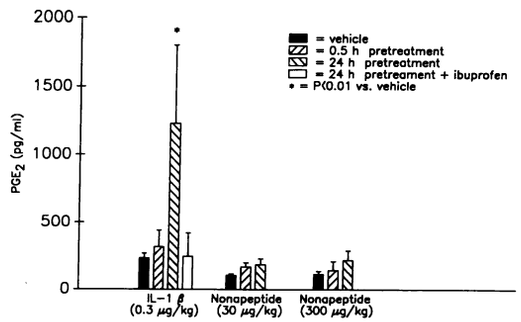

Figure 2. Effect of IL-1β and the 163–171 fragment of human IL-1β on PGE_2 production in rabbit colon. PGE_2 was measured in rectal dialysis immediately before induction of colitis. Compared with placebo administration (*solid bars*) 24-h pretreatment with IL-1β significantly enhanced PGE_2 production. Administration of ibuprofen together with 24-h IL-1β pretreatment (*open bars*) blocked the increase in PGE_2. IL-1β 0.5-h pretreatment and the 163–171 nonapeptide at either 0.5- or 24-h pretreatment did not alter PGE_2 production.

Acknowledgments

We thank Marjorie Lee for technical assistance.

This work was supported in part by grant DK-36869 from the National Institutes of Health. Dr. Cominelli is a visiting scientist from Istituto di Clinica Medica II, University of Florence, Italy, and a recipient of a Fellowship Award of the Blinder Foundation for Crohn's disease.

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