Proc. Natl. Acad. Sci. USA
Vol. 85, pp. 2315–2319, April 1988
Medical Sciences

Enhancement of acute allergic inflammation by indomethacin is reversed by prostaglandin E_2: Apparent correlation with *in vivo* modulation of mediator release

(hamster cheek pouch/microcirculation/mast cells/histamine release/leukotrienes)

JOHAN RAUD*†‡, SVEN-ERIK DAHLÉN*†, ANITA SYDBOM§, LENNART LINDBOM*†, AND PER HEDQVIST*†

Departments of *Physiology I and §Pharmacology, Karolinska Institutet, and the †National Institute of Environmental Medicine, S-104 01, Stockholm, Sweden

Communicated by Bengt Samuelsson, November 23, 1987

ABSTRACT **Intravital microscopy and determination of *in vivo* histamine release revealed that the cyclooxygenase inhibitor indomethacin reduced antigen-induced vasodilation while enhancing plasma extravasation, leukocyte accumulation, and histamine release in cheek pouches of immunized hamsters. Topical application of prostaglandin E_2 (PGE_2, 30 nM) totally reversed the indomethacin-induced potentiation of the inflammatory reaction to antigen challenge and suppressed both the histamine release and plasma leakage also in the absence of indomethacin. On the other hand, PGE_2, which *per se* caused vasodilation, markedly potentiated the postcapillary leakage of plasma induced by histamine or leukotriene C_4, as well as the leukocyte activation and subsequent plasma extravasation evoked by leukotriene B_4. Taken together, the data indicate that PGE_2 reduced the antigen response by suppression of mediator release from the numerous mast cells present in the cheek pouch. Moreover, the PGE_2-sensitive potentiation by indomethacin of the antigen response suggests that endogenous vasodilating prostaglandins (possibly PGE_2) predominantly were anti-inflammatory.**

The potent vasodilator prostaglandin E_2 (PGE_2) is released at sites of inflammation, causes a wheal and flare reaction when injected into skin, and enhances the effects of pain- and edema-producing stimuli (cf. ref. 1). Moreover, nonsteroidal antiinflammatory drugs (NSAIDs) inhibit the fatty acid cyclooxygenase, which catalyzes the initial steps in the biosynthesis of PGE_2 from arachidonic acid (cf. ref. 1). Hence, PGE_2 is considered to be an inflammatory mediator. Nevertheless, PGE_2 and related compounds also exhibit antiinflammatory activities (2–8), and NSAIDs sometimes augment inflammation (9, 10). These conflicting observations complicate understanding of the functional role of PGE_2 in inflammation.

In the present study, intravital microscopy of the hamster cheek pouch was used to characterize the influence of PGE_2 and the prototype of NSAIDs, indomethacin, on microcirculatory dynamics during acute mast cell-dependent inflammation evoked by antigen challenge. Supported also by *in vivo* measurements of antigen-induced histamine release from the cheek pouch and analysis of the microvascular interactions between exogenous inflammatory mediators and PGE_2, we conclude that endogenous cyclooxygenase products predominantly inhibit acute allergic inflammation via local suppression of inflammatory mediator release.

MATERIALS AND METHODS

Drugs and Chemicals. Leukotrienes B_4 and C_4 (LTB_4, LTC_4) were provided by J. Rokach (Merck Frosst Labs, Pointe Claire, PQ) and PGE_2 by J. Pike (Upjohn). Arachidonic acid was from Nu Chek Prep. Stock solutions of LTB_4, PGE_2, and arachidonic acid were stored at −20°C in ethanol, and LTC_4 was stored similarly in ethanol/water, 1:1. Concentrations and purity of the icosanoids were checked before use by appropriate methods (UV spectrometry, reverse-phase HPLC, and thin-layer chromatography). Acetylcholine chloride, fluorescein isothiocyanate-conjugated dextran (FITC-dextran, M_r 150,000), histamine dihydrochloride, ovalbumin (grade III), and pyrilamine maleate (mepyramine) were from Sigma, indomethacin hydrochloride was from Merck, and aluminum hydroxide [$Al(OH)_3$, dried gel, F2200] was from Reheis (Kankakee, IL).

Animals and Immunization. Male Syrian hamsters (80–100 g) were immunized by i.p. injections of 10 μg of ovalbumin in 0.2 ml of saline containing 10 mg of $Al(OH)_3$. Four weeks later the animals were reinjected with 1 μg of ovalbumin in 10 mg of $Al(OH)_3$ i.p., and the experiments were done 7–10 days after the second injection.

Cheek Pouch Preparation and Intravital Microscopy. As described (11), the left cheek pouch of anesthetized hamsters was everted and prepared for intravital microscopy under continuous superfusion (7 ml/min) with a modified Krebs solution maintaining physiological temperature, pH, and gas tensions.

The microvascular network in the exposed cheek pouch was observed with a Leitz Orthoplan microscope equipped with ×10 oculars, ×4 long-distance lens (for plasma extravasation), and ×25 or ×55 water-immersion lenses (for vessel diameters and leukocytes). The preparation was transilluminated with a halogen 12-V 100-W lamp or a mercury short arc 100-W lamp with proper filters for ordinary light and fluorescent light observations, respectively.

Plasma extravasation was measured using FITC-dextran (25 mg per 100 g of body weight, i.v.) as a tracer for plasma proteins and by counting the number of fluorescent leakage sites per cm^2 of cheek pouch area (12). Total leakage over a given time period was estimated by integration of the area under the curve (obtained by determinations of leakage sites every 5 min).

Arteriolar diameters were measured in segments with an i.d. of 14.1 ± 2.7 μm (mean ± SD, n = 50). The number of leukocytes marginating (slowly rolling along) and adhering (being fixed) to the venular endothelium, collectively referred to as endothelial leukocytes, was quantitated in venules with an i.d. of 25.8 ± 6.4 μm (n = 35). In each experiment, the number of endothelial leukocytes, before and 40 min after challenge with ovalbumin or LTB_4, were counted in seven separate 190-μm-long venular segments (col-

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: FITC-dextran, fluorescein isothiocyanate-conjugated dextran; LTB_4, leukotriene B_4; LTC_4, leukotriene C_4; NSAID, nonsteroidal antiinflammatory drug; PGE_2, prostaglandin E_2.

‡To whom reprint requests should be addressed.

lectively = 1 unit of area). The number of emigrated leukocytes within a 190 × 140-μm frame around the same seven venules were also determined (collectively = 1 unit of area). Vessel diameters and leukocyte numbers were watched on a TV monitor via a videocamera (Panasonic WV-1550) and stored on videotape with a Sony VO-5630 videocassette recorder for subsequent detailed analysis.

A Leitz (Vario Ortomat 2) automatic microscope camera and Kodak Ektachrome P800/1600 daylight film exposed at 1600 ASA were used for micrographs.

Experimental Design. Twenty min after i.v. injection of FITC-dextran, the cheek pouches were challenged topically (drugs added to superfusate) with ovalbumin, histamine, or LTB_4 for 5 min and with arachidonic acid or LTC_4 for 3 min. Substances were diluted to give a final concentration of ethanol <0.05%, which itself has no effects on the microvascular variables studied.

Indomethacin (5 mg/kg) was given i.v. 40 min before challenge. Topical treatment with indomethacin (6 μM) and mepyramine (15 μM) was administered throughout the experiments, starting 15 min before challenge. Prostaglandin E_2 (30 nM) was given topically for 15 min, starting 5 min before challenge.

Histamine Release The amount of histamine liberated to the buffer surrounding the cheek pouch was measured under the experimental conditions prevailing for the microscopic observation of the microcirculation (FITC-dextran excluded). The superfusion buffer (≈2.5 ml) was collected under stop-flow conditions for two successive 5-min periods (before and during antigen challenge) and immediately frozen. Histamine content (expressed as histamine base) was assayed fluorometrically in duplicate samples, as described (13)—however, omitting the extraction procedure. Cheek pouch tissue corresponding to the area in contact with the sampled buffer fluid was excised and weighed at the end of the experiments.

Statistical Analysis. Statistical evaluations were done using the Mann–Whitney U test; data are expressed as mean values ± SD.

RESULTS

Ovalbumin Challenge. A 5-min topical challenge with ovalbumin (10 μg/ml) provoked an acute inflammatory response in cheek pouches of immunized hamsters. After brief segmental constriction of arterioles, extensive extravasation of FITC-dextran (marker for plasma-protein leakage) occurred in parallel with arteriolar dilation (Figs. 1 and 2). After ≈5 min, an increase of slowly marginating and adhering leukocytes was seen in venules of all sizes (i.d. ≈10–60 μm). Leukocyte accumulation was sustained, and 40 min after challenge, the number of endothelium-associated leukocytes remained elevated (214 ± 84% of prechallenge value, mean ± SD, $n = 5$, $P < 0.01$). Emigration of leukocytes to the perivascular space was sparse, however.

During the first few minutes of ovalbumin challenge, leakage of plasma occurred predominantly from postcapillary venules (i.d. ≈ 10 μm). Subsequently, leakage also developed along larger venules (i.d. ≥ 20 μm) and appeared to correlate with the increased leukocyte–endothelium interactions.

As in previous observations (14), pretreatment with the histamine antagonist mepyramine (15 μM topically) abolished postcapillary leakage induced by supramaximal doses of histamine (10 μM) and substantially blocked the early (0–5 min) leakage of plasma provoked by ovalbumin in immunized animals ($n = 6$) (data not shown). On the other hand, the delayed leukocyte-associated leakage (peak at 10 min) after ovalbumin challenge still occurred in the presence of mepyramine (data not shown). Mepyramine did not alter the vasodilation induced by 1 μM acetylcholine (data not shown).

Potentiation by Indomethacin of the Response to Ovalbumin. Pretreatment with indomethacin (5 mg/kg i.v. and 6 μM topically) greatly increased and prolonged the leakage of plasma induced by ovalbumin (Figs. 1–3). The potentiated leakage was particularly prominent in larger venules, which also exhibited a markedly enhanced accumulation of leukocytes. Thus, at 40 min after ovalbumin the number of endothelial leukocytes was 255% of that in animals challenged by ovalbumin alone, and the emigration of leukocytes was enhanced by >1500% (Fig. 3).

Although the potentiating effect of indomethacin seemed most prominent during the later phase (>10 min) of plasma leakage (Fig. 2), indomethacin also potentiated the early phase (<10 min) of leakage, but this enhancement mainly appeared as increase in size and intensity of the leakage sites, rather than as increase in site number (Fig. 1). Furthermore, indomethacin also greatly potentiated the response to ovalbumin in mepyramine-treated animals, in which total leakage (0–40 min) was enhanced by 216 ± 110% ($n = 5$, $P < 0.01$) as compared with animals challenged with mepyramine alone.

Note that indomethacin reduced the vasodilation evoked by ovalbumin (Fig. 2) and prevented the arteriolar dilation induced by topical application of arachidonic acid (30 μM) (Table 1). Except for a slight increase in the prechallenge number of endothelial leukocytes, indomethacin had no influence on arteriolar dilation induced by acetylcholine or histamine, the postcapillary leakage response to histamine, or the basal emigration of leukocytes (Table 1).

Inhibition by PGE_2 of the Ovalbumin Responses. PGE_2 (30 nM topically), which *per se* induced marked vasodilation (≈100% increase of arteriolar diameter), caused >30% inhibition of the early, predominantly histamine-dependent, postcapillary extravasation of plasma in animals challenged with ovalbumin (Fig. 2).

Moreover, PGE_2 completely reversed the indomethacin-induced potentiation of plasma extravasation (Fig. 3), including the size and intensity of the leakage sites. In this case, PGE_2 also effectively reversed the enhanced number of endothelial and emigrated leukocytes after indomethacin treatment (Fig. 3).

Synergism Between PGE_2 and Inflammatory Mediators. LTC_4 (10 nM) caused a transient reduction of arteriolar diameter to 40.5 ± 11.5% of prechallenge diameter ($P < 0.05$) and a substantial increase in the number of leakage sites at postcapillary venules. PGE_2 (30 nM) prevented LTC_4-induced vasoconstriction, while causing a marked potentiation of the leakage response (Fig. 4).

Histamine (2 μM topically) also induced postcapillary leakage of plasma (145 ± 45 leakage sites per cm^2 at 5 min after start of challenge, $n = 4$). Although histamine itself caused arteriolar dilation, PGE_2 (30 nM) caused further dilation and potentiated the histamine-induced leakage response to 397 ± 30 leakage sites per cm^2 at 5 min ($n = 3$, $P < 0.05$).

LTB_4 (20 nM), did not affect arteriolar diameter, but induced a leukocyte-associated leakage of plasma from both postcapillary and larger venules. When LTB_4 was applied in the presence of PGE_2 (30 nM), both plasma leakage (Fig. 4) and the number of endothelial and emigrated leukocytes were markedly potentiated (Fig. 5).

Effects of PGE_2 and Indomethacin on Ovalbumin-Induced Histamine Release. The potentiating effect of PGE_2 on the responses to exogenous mediators indicated that PGE_2 suppressed the responses to ovalbumin at the level of mediator release. This interpretation gained substantial support by determination of *in vivo* histamine release under the present experimental conditions (Table 2). Thus, ovalbumin caused a detectable net release of histamine from the cheek pouch. This release of histamine was reduced by almost 60% in the

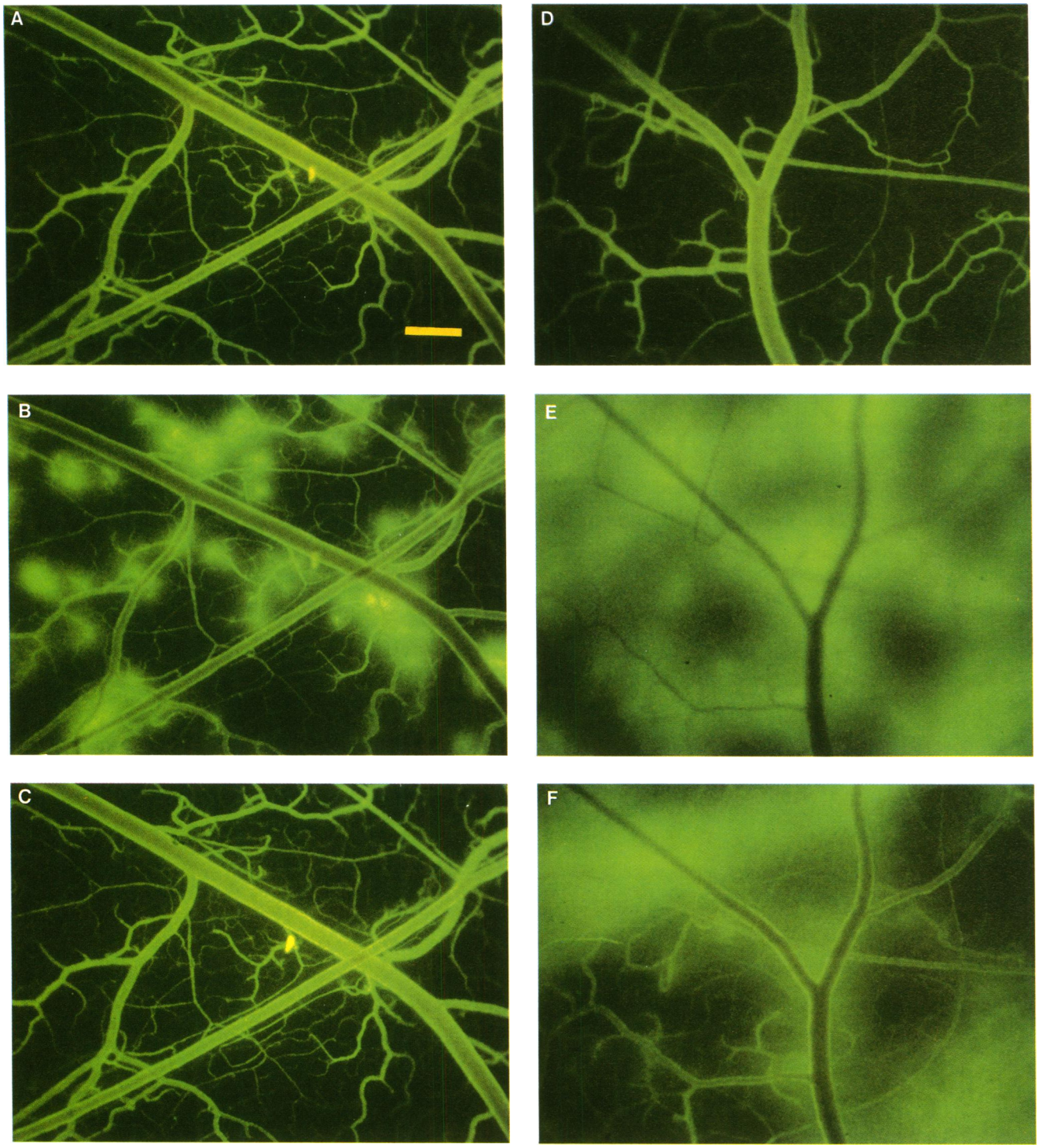

FIG. 1. Microvasculature in cheek pouches of immunized hamsters. (*A–C*) Before, 8 min after, and 30 min after start of topical challenge with specific antigen ovalbumin (10 μg/ml for 5 min), which evokes reversible leakage of plasma (FITC-dextran), predominantly from postcapillary venules. (*D–F*) Same procedure and time sequence in animal pretreated with indomethacin. Note enhanced and prolonged leakage response and that the response also involves large venules. (Bar = 200 μm.)

presence of PGE_2 (30 nM). On the other hand, indomethacin enhanced release of histamine by >60%. Finally, PGE_2 effectively suppressed this potentiation ($P < 0.01$).

DISCUSSION

From evidence principally obtained by direct observation of the sequence of microvascular events that follow challenge with antigen (ovalbumin) or individual inflammatory mediators, our investigation in the hamster cheek pouch preparation shows that endogenous vasodilating prostaglandins may suppress acute allergic inflammation by inhibiting inflammatory mediator release.

First, the cyclooxygenase inhibitor indomethacin strikingly potentiated the antigen-induced leakage of plasma and accumulation of leukocytes. The effect of indomethacin appeared specific in that basal vascular permeability as well as the vascular reactivity to histamine and acetylcholine

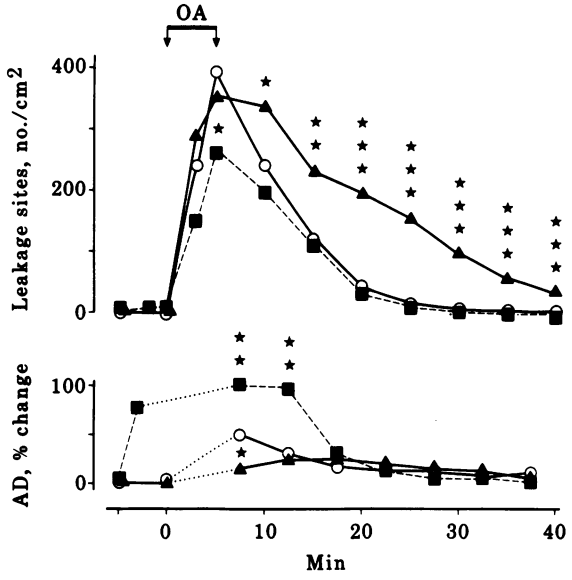

FIG. 2. Time course for plasma leakage and changes in arteriolar diameter (AD) after topical antigen challenge with ovalbumin (OA) (10 μg/ml for 5 min) in hamster cheek pouch. ○, OA alone; ▲, OA plus indomethacin (5 mg/kg i.v. and 6 μM topically); -■-, OA plus PGE_2 (30 nM topically, −5 to +10 min). ..., Arteriolar diameter not measured during segmental vasoconstriction. Mean values, n = 5–7. ★, $P < 0.05$; ★★, $P < 0.01$; ★★★, $P < 0.001$ vs. OA alone.

were unaffected by this drug. Also, the effects of LTB_4 and LTC_4 on microvascular permeability in the cheek pouch are known to be unchanged by indomethacin (15). Furthermore, indomethacin prevented arachidonic acid-induced vasodilation, which together with other reports (cf. refs. 1, 9) indicates that our dosage of indomethacin effectively inhibited cyclooxygenase activity. Additionally, diclofenac, another cyclooxygenase inhibitor, also enhances acute allergic inflammation in the hamster cheek pouch (unpublished data).

Second, topical application of PGE_2 (30 nM) reduced the inflammatory responses evoked by antigen. In animals challenged only with ovalbumin, inhibition particularly affected the early and predominantly histamine-dependent leakage of plasma from postcapillary venules. However, when the antigen response was enhanced by indomethacin, PGE_2 caused profound suppression also of the plasma extravasation associated with leukocyte emigration. This suppression by PGE_2 of leukocyte emigration, in fact, correlated with the

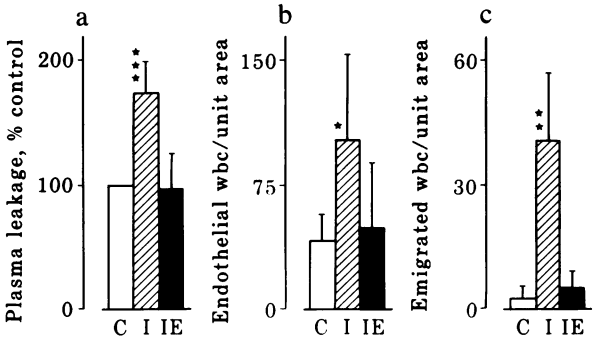

FIG. 3. Total (0–40 min) leakage of plasma (*a*), and number of endothelial (*b*) and emigrated (*c*) leukocytes (wbc) 40 min after challenge with specific antigen (ovalbumin, 10 μg/ml for 5 min) in hamster cheek pouch. C, ovalbumin alone; I, ovalbumin plus indomethacin (5 mg/kg i.v. and 6 μM topically); IE, ovalbumin plus indomethacin plus PGE_2 (30 nM topically, −5 to +10 min). Mean values ± SD, n = 5–7. ★, $P < 0.05$; ★★, $P < 0.01$; and ★★★, $P < 0.001$ vs. ovalbumin alone.

Table 1. Effects of indomethacin (5 mg/kg i.v. and 6 μM topically) on microvascular events in hamster cheek pouch

	Control	Indomethacin
Arteriolar diameter (% change)		
Arachidonic acid (30 μM)	103 ± 41 (4)	−10 ± 16 (4)*
Acetylcholine (1 μM)	81 ± 9 (13)	69 ± 28 (13)
Histamine (10 μM)	61 ± 38 (7)	79 ± 29 (3)
Leakage sites after 10 μM histamine, maximal no.	374 ± 149 (7)	355 ± 41 (3)
Endothelial leukocytes, no.	35 ± 12 (10)	48 ± 15 (11)*
Extravascular leukocytes, no.	5 ± 7 (10)	8 ± 3 (11)

Mean values ± SD. n = number of experiments.
*$P < 0.05$ vs. control.

inhibition of plasma leakage. Moreover, the effect of PGE_2 in animals given indomethacin virtually indicated restitution. It is noteworthy that indomethacin-sensitive release of endogenous E-type prostaglandins has been reported in the hamster cheek pouch (12), and that indomethacin reduced the vasodilation induced by challenge with ovalbumin (this paper).

Third, contrary to inhibition of antigen-induced reactions, PGE_2 enhanced the responses to three exogenously applied inflammatory mediators with different profiles of action on the microvasculature (histamine, LTB_4, and LTC_4). Although these observations agree with previous reports that vasodilator prostaglandins, including PGE_2, potentiate responses to inflammatory mediators (16, 17), they further support the idea that PGE_2 suppressed antigen responses by an action exerted at the level of mediator release.

Fourth, by determination of histamine release from the cheek pouch, the present pharmacological manipulations (PGE_2 and indomethacin) were documented as modulating histamine liberation *in vivo*. Because ovalbumin causes pronounced degranulation of the numerous mast cells in the cheek pouch of immunized hamsters (unpublished observation), the detected histamine is most likely derived from these cells. Previous *in vitro* studies showed that histamine release from various tissues, including mast cells, can be suppressed by E-type prostaglandins (4, 8, 18) and enhanced by NSAIDs (18–20). Our results show that this mechanism also operates under *in vivo* conditions. Moreover, the complete reversal by PGE_2 in low concentration (30 nM) of the

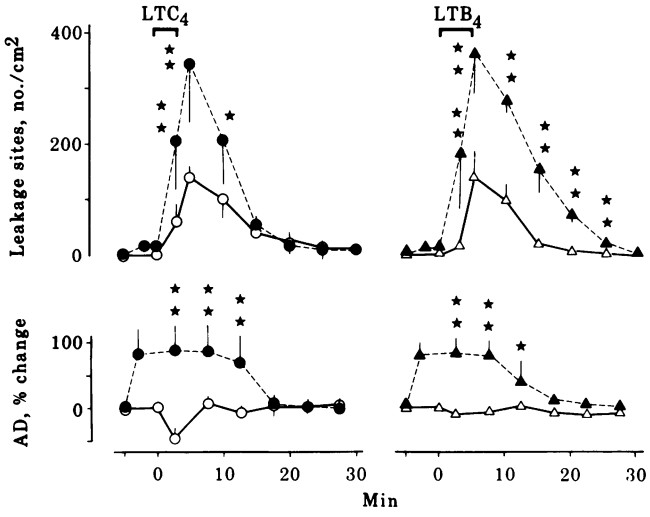

FIG. 4. Time course for plasma leakage and changes in arteriolar diameter (AD) in cheek pouches of nonimmunized hamsters. Topical application of LTC_4 (10 nM) and LTB_4 (20 nM) alone (open symbols), or in the presence of PGE_2 (30 nM topically, −5 to +10 min) (closed symbols). Mean values ± SD, n = 4–5. ★, $P < 0.05$; ★★, $P < 0.01$.

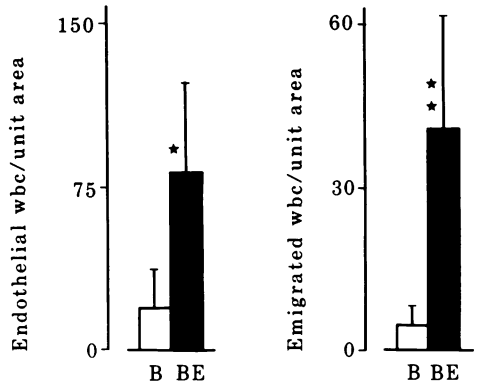

FIG. 5. Number of endothelial and emigrated leukocytes (wbc) 40 min after topical challenge with LTB_4 (20 nM) (B) and LTB_4 in the presence of PGE_2 (30 nM topically, −5 to +10 min) (BE) in hamster cheek pouch. Mean values ± SD, $n = 5$. ★, $P < 0.05$, ★★, $P < 0.01$.

potentiating effect of indomethacin on antigen-induced inflammation advocates a regulatory function on mediator release for endogenous PGE_2. In addition, we emphasize that this local mechanism governing mediator release from cells at the site of inflammation differs from the intervention in inflammatory reactions by systemically administered prostaglandins (2, 6, 21), where inhibition has been attributed to lowering of systemic blood pressure and/or functional alterations of circulating leukocytes (21).

Modulation of antigen-induced histamine release may explain how PGE_2 and indomethacin altered the early leakage of plasma induced by antigen. Because indomethacin enhanced the postcapillary leakage to ovalbumin also in mepyramine-treated animals, modulated release of other mediators such as leukotrienes C_4, D_4, and E_4 may have contributed, as indicated by studies *in vitro* (18, 20, 22, 23). However, neither histamine nor cysteinyl-leukotrienes mediate the leukocyte accumulation and associated leakage of plasma enhanced by indomethacin, a phenomenon predicted to require increased release of chemotactic mediator(s). The nature of such a mediator(s) remains elusive, but from the documented modulation of histamine release, the lines of evidence discussed above, and *in vitro* data for secretion from leukocytes (7), it is tempting to propose that PGE_2 also modulated the release of chemotactic mediators. Interestingly enough, in other *in vivo* models for inflammatory or anaphylactic reactions (9, 24), cyclooxygenase inhibition has been suggested to enhance the release of a chemotactic 5-lipoxygenase product, or specifically LTB_4. However,whether or not PGE_2 and indomethacin affect release of chemotactic factors from the hamster cheek pouch remains to be shown.

Table 2. Antigen-induced release of histamine in hamster cheek pouch

Treatment	*n*	Basal release, pmol/mg of tissue	OA-induced release, pmol/mg of tissue
Control	5	1.3 ± 0.5	6.5 ± 2.0
PGE_2	5	1.3 ± 0.8	2.7 ± 1.3*
Indomethacin	5	1.6 ± 0.3	10.6 ± 3.8*
Indomethacin + PGE_2	6	0.7 ± 0.2	4.5 ± 2.3

Mean values ± SD of histamine content (in units per wet weight of tissue) in surrounding buffer after two consecutive 5-min periods before (basal) and during antigen challenge [ovalbumin (OA), 10 μg/ml topically], in the presence of indomethacin (5 mg/kg i.v. and 6 μM topically) and/or PGE_2 (30 nM topically).
*$P < 0.05$ vs. control.

Considered together, dual action of local PGE_2 in the hamster cheek pouch, inhibition of mediator release, and enhancement of mediator action demonstrate that PGE_2 can exert both anti- and proinflammatory activities in one and the same model. However, in this model of mast cell-dependent inflammation, the influence of PGE_2 and indomethacin on the release of inflammatory mediators predominated. Probably variables such as the degree of local blood flow, the site of prostaglandin production, or the condition of the tissue (healthy, inflamed, etc.) contribute to the final result in other instances. Nevertheless, this dual *in vivo* action of prostaglandins may help explain conflicting effects of NSAIDs and prostaglandins in different models for inflammation.

Supported by grants from the Knut and Alice Wallenberg Foundation, the Swedish Medical Research Council (14X-4342, 03P-6949), the National Association Against Heart and Chest Diseases, the National Institute of Environmental Medicine, the Swedish Association Against Asthma and Allergy, King Gustav V's Research Foundation, and Karolinska Institutet.

1. Ferreira, S. H. & Vane, J. R. (1979) in *Anti-Inflammatory Drugs*, eds. Vane, J. R. & Ferreira, S. H. (Springer, Berlin), pp. 348–398.
2. Aspinall, R. L. & Cammarata, P. S. (1969) *Nature (London)* **224**, 1320–1321.
3. Koopman, W. J., Orange, R. P. & Austen, K. F. (1971) *Proc. Soc. Exp. Biol. Med.* **137**, 64–67.
4. Lichtenstein, L. M. & Bourne, H. R. (1971) in *Biochemistry of Acute Allergic Reactions: Second International Symposium*, eds. Austen, K. F. & Becker, E. L. (Blackwell, Oxford), pp. 161–174.
5. Weissmann, G., Smolen, J. E. & Korchak, H. (1980) in *Advances in Prostaglandin and Thromboxane Research*, eds. Samuelsson, B., Ramwell, P. W. & Paoletti, R. (Raven, New York), Vol. 8, pp. 1637–1653.
6. Fantone, J. C., Kunkel, S. L., Ward, P. A. & Zurier, R. B. (1980) *J. Immunol.* **125**, 2591–2596.
7. Ham, E. A., Soderman, D. D., Zanetti, M. E., Dougherty, H. W., McCauley, E. & Kuehl, F. A., Jr. (1983) *Proc. Natl. Acad. Sci. USA* **80**, 4349–4353.
8. Kaliner, M. & Austen, K. F. (1974) *J. Immunol.* **112**, 664–674.
9. Higgs, G. A., Eakins, K. E., Mugridge, K. G., Moncada, S. & Vane, J. R. (1980) *Eur. J. Pharmacol.* **66**, 81–86.
10. Hedqvist, P., Dahlén, S.-E. & Palmertz, U. (1984) *Prostaglandins* **28**, 605–608.
11. Björk, J., Smedegård, G., Svensjö, E. & Arfors, K.-E. (1984) *Prog. Appl. Microcirc.* **6**, 41–53.
12. Svensjö, E., Arfors, K.-E., Arturson, G. & Rutili, G. (1978) *Upsala J. Med. Sci.* **83**, 71–79.
13. Shore, P. A., Burkhalter, A. & Cohn, V. H., Jr. (1959) *J. Pharmacol. Exp. Ther.* **127**, 182–186.
14. Raud, J., Dahlén, S.-E., Smedegård, G. & Hedqvist, P. (1986) *Int. J. Microcirc. Clin. Exp.* **5**, 123 (abstr.).
15. Björk, J., Dahlén, S.-E., Hedqvist, P. & Arfors, K.-E. (1983) in *Advances in Prostaglandin, Thromboxane, and Leukotriene Research*, eds. Samuelsson, B., Paoletti, R. & Ramwell, P. (Raven, New York), Vol. 12, pp. 1–6.
16 Williams, T. J. & Peck, M. J. (1977) *Nature (London)* **270**, 530–532.
17. Bray, M. A., Cunningham, F. M., Ford-Hutchinson, A. W. & Smith, M. J. H. (1981) *Br. J. Pharmacol.* **72**, 483–486.
18. Hitchcock, M. (1978) *J. Pharmacol. Exp. Ther.* **207**, 630–640.
19. Okazaki, T., Ilea, V. S., Rosario, N. A., Reisman, R. E., Arbesman, C. E., Lee, J. B. & Middleton, E., Jr. (1977) *J. Allergy Clin. Immunol.* **60**, 360–366.
20. Engineer, D. M., Niederhauser, U., Piper, P. J. & Sirois, P. (1978) *Br. J. Pharmacol.* **62**, 61–66.
21. Rampart, M. & Williams, T. J. (1986) *Am. J. Pathol.* **124**, 66–73.
22. Walker, J. L. (1973) in *Advances in the Biosciences*, eds. Bergström, S. & Bernhard, S. (Pergamon, New York), Vol. 9, pp. 235–240.
23. Burka, J. F. & Eyre, P. (1975) *Int. Arch. Allergy Appl. Immunol.* **49**, 774–781.
24. Lee, T. H., Israel, E., Drazen, J. M., Leitch, A. G., Ravalese, J., III, Corey, E. J., Robinson, D. R., Lewis, R. A. & Austen, K. F. (1986) *J. Immunol.* **136**, 2575–2582.