Br. J. Pharmacol. (1990), **99**, 449–454

Vasodilatation and inhibition of mediator release represent two distinct mechanisms for prostaglandin modulation of acute mast cell-dependent inflammation

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1 Intravital microscopy of the hamster cheek pouch was used to examine the influence of vasodilator prostanoids (prostaglandin E_2 (PGE_2), PGI_2), forskolin, and nitroprusside on the microvascular changes during acute inflammation induced by antigen or histamine. The results extend our previous finding that PGE_2 modulates allergic inflammation and histamine release in the cheek pouch model.

2 The microvascular actions of arachidonic acid and different cyclo-oxygenase products (PGE_2, PGD_2, PGI_2, $PGF_{2\alpha}$, and the thromboxane A_2 (TXA_2)-analogue U-44069) were first compared with respect to their effects on arteriolar tone. Of the prostaglandins, only PGE_2 and PGI_2 were potent vasodilators and markedly increased local blood flow. Nitroprusside and forskolin also caused vasodilatation and increased blood flow, but were somewhat less potent than PGE_2 and PGI_2.

3 Topically applied PGE_2 and PGI_2 in vasodilator concentrations suppressed the antigen-induced plasma leakage. On the other hand, although the antigen response was predominantly mediated by histamine, both prostaglandins enhanced the plasma leakage evoked by exogeneous histamine.

4 In contrast, the vasodilator nitroprusside, in a dose causing an increase in blood flow equal to that of PGE_2 and PGI_2, potentiated both the histamine-induced plasma leakage, as well as the plasma and leukocyte extravasation after antigen challenge, indicating that the anti-inflammatory actions of the prostaglandins were unrelated to their vasodilator properties *per se*.

5 Because forskolin, a specific activator of adenylate cyclase, mimicked the actions of PGE_2 and PGI_2, i.e. inhibition of the antigen-induced plasma extravasation and enhancement of the histamine response, it is possible that the observed antiallergic effects of the prostaglandins were related to accumulation of intracellular adenosine 3′:5′-cyclic monophosphate (cyclic AMP).

6 Taken together, there appears to be a competition between pro- and anti-inflammatory effects of PGE_2 and PGI_2 in reactions involving release of endogeneous inflammatory mediators *in vivo*, i.e. enhancement of inflammatory mediator target action on one hand ('two mediator synergism'), and suppression of mediator release on the other. Moreover, the observations indicate that vasodilatation and inhibition of mediator release are two distinct actions of PGE_2 and PGI_2.

Introduction

Since the observation that nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin formation (Vane, 1971; Smith & Willis, 1971; Ferreira *et al.*, 1971), considerable interest has focused on the involvement of prostaglandins and related compounds in inflammation. Prostaglandins of the E series (PGE_2, PGE_1) and prostacyclin (PGI_2) have generally been regarded as proinflammatory mediators because they are potent vasodilators and act synergistically with other inflammatory mediators (see Williams, 1983). However, there are also instances when these prostaglandins display actions which must be regarded as anti-inflammatory. For example, *in vitro* PGEs and PGI_2 may inhibit evoked release of inflammatory mediators from granulocytes (Lichtenstein & Bourne, 1971; Weissmann *et al.*, 1980; Camussi *et al.*, 1981; Ham *et al.*, 1983), mast cells (Loeffler *et al.*, 1971; Kaliner & Austen, 1974; Peachell *et al.*, 1988) and lung tissue (Walker, 1973; Hitchcock, 1978; Engineer *et al.*, 1978), with adenosine 3′:5′-cyclic monophosphate (cyclic AMP) suggested to act as the second messenger.

We have previously shown that intravital microscopy of the hamster cheek pouch can be used for studies of microvascular dynamics and *in vivo* histamine release during antigen-induced mast cell-dependent inflammation (Raud *et al.*, 1988; 1989a,b). In this model, topical administration of PGE_2 in vasodilator concentrations has been found to reduce significantly both histamine release and plasma extravasation evoked by antigen challenge (Raud *et al.*, 1988). On the other hand, the NSAIDs indomethacin and diclofenac enhance histamine release, plasma leakage, and leukocyte accumulation evoked by challenge with antigen or the mast cell secretagogue compound 48/80 in the check pouch (Raud *et al.*, 1988; 1989c). Moreover, PGE_2 effectively reverses the NSAID-induced potentiation of histamine release and inflammation (Raud *et al.*, 1988; 1989c). These observations support the view that endogenous vasodilator prostanoids may function as local regulators of mediator secretion in the hamster cheek pouch, and possibly also in other experimental models where NSAIDs have been shown to enhance inflammation (Higgs *et al.*, 1980; Hedqvist *et al.*, 1984; Lundberg & Gerdin, 1984). Nevertheless, it is evident that PGE_2 also exerts proinflammatory actions in the hamster cheek pouch, because plasma extravasation induced by challenge with exogenous inflammatory mediators is increased in the presence of topically applied PGE_2 in vasodilator concentrations. This potentiating effect of PGE_2 includes the plasma leakage from postcapillary venules produced by directly acting mediators such as histamine and leukotriene C_4, (LTC_4), as well as leukocyte-dependent plasma extravasation in response to LTB_4 (Raud *et al.*, 1988). Taken together, there appears to be a competition between pro- and anti-inflammatory effects of PGE_2 in reactions involving release of endogenous inflammatory mediators *in vivo*, i.e. enhancement of mediator target action on one hand, and suppression of mediator release on the other.

Prompted by the observations described above, the present study addresses two major questions: (1) Is the inhibition of the antigen response previously documented for PGE_2 a consequence of the vasodilatation *per se* or is it related to other factors such as cyclic AMP elevation? (2) Are there vasodilator cyclo-oxygenase products other than PGE_2 which may contribute to inhibition of antigen-induced inflammation in

the cheek pouch? Therefore, the microvascular actions in this particular model of the primary cyclo-oxygenase products PGE_2, PGD_2, PGI_2, $PGF_{2\alpha}$ and thromboxane A_2 (TXA_2, e.g. its analogue U-44069) were first compared with respect to their effects on arteriolar tone, and, as expected, only PGI_2 shared the vasodilator action of PGE_2. Thereafter, the relationship between vasodilatation (and increased blood flow) and effects on histamine or antigen-induced responses was investigated by comparing the influence of PGE_2 and PGI_2 with that of two structurally and pharmacodynamically different vasodilators, namely the cyclic AMP elevating agent forskolin (Seamon *et al.*, 1981) and nitroprusside which triggers cyclic GMP production (Rapoport & Murad, 1983).

The present observations support the view that vasodilator prostaglandins (i.e. PGE_2 and PGI_2) can inhibit mast cell-dependent inflammation by an action that is unrelated to vasodilatation and increased blood flow, but rather involves local suppression of mediator secretion, as previously documented for PGE_2 (Raud *et al.*, 1988). In addition, it is possible that the anti-inflammatory actions of these prostaglandins *in vivo* occur via induction of intracellular cyclic AMP accumulation.

Methods

Animals and immunization

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

Cheek pouch preparation and intravital microscopy

As described in detail elsewhere (Björk *et al.*, 1984), the left cheek pouch of anaesthetized (sodium pentobarbitone 6 mg $100\,g^{-1}$ body weight, i.p.) hamsters was everted and prepared for intravital microscopy under continuous superfusion ($7\,ml\,min^{-1}$) with a bicarbonate buffer maintaining physiological temperature, pH and gas tensions.

The exposed microvascular network in the cheek pouch was observed with a Leitz Orthoplan microscope equipped with × 10 oculars, a × 4 long-distance lens (for plasma extravasation), and × 25 or × 55 water immersion lenses (for vessel diameters and leukocyte emigration). 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 quantified by use of FITC-dextran (25 mg $100\,g^{-1}$ of body weight was given i.v. as a $50\,mg\,ml^{-1}$ saline solution) as a tracer for plasma proteins and by counting the number of fluorescent leakage sites per cm^2 of cheek pouch area (Svensjö *et al.*, 1978). Total plasma leakage over a given time period was estimated by determining the area under the curve for the FITC-dextran leakage sites.

Vessel diameters and leukocyte actions were visualized on a TV monitor via a videocamera (Panasonic Wv-1550) and stored on videotape with a SONY VO-5630 videocasette recorder for subsequent measurement. Arteriolar diameters and blood flow were measured in vascular segments with an inner diameter of 13 ± 2.1 μm. Arteriolar erythrocyte velocity was measured on-line in single arterioles according to the dual-slit cross-correlation technique (Wayland & Johnson, 1967), and volume blood flow was calculated from the velocity data and the simultaneous values for arteriolar diameter measured off-line from the video recordings. In the experiments with antigen (ovalbumin) or LTB_4 challenge, leukocyte emigration around venules with an inner diameter of 30 ± 4.1 μm was quantitated from video recordings. The number of extravascular leukocytes was counted before and 40 min after challenge within a 190 × 140 μm frame around 7 venular segments (collectively designated 1 unit area).

Experimental design

After completion of the cheek pouch preparation, FITC-dextran was injected, and the responsiveness of the preparation to acetylcholine was assessed according to Duling (1973). The arterioles used for examination of changes in diameter and blood flow responded to acetylcholine (1 μM topically for 30 s) with prompt dilatation which lasted less than 2 min. No increase in microvascular permeability or signs of leukocyte activation were observed after acetylcholine. Ten min later the preparation was challenged topically (drugs added to superfusate to reach indicated concentrations around the cheek pouch) with ovalbumin, histamine, or LTB_4, either alone or in the presence of a given vasodilator (durations and concentrations given in text). Mepyramine was given topically throughout the experiments, starting 15 min before challenge. Substances dissolved in ethanol were diluted in the buffer solution to give a final concentration of ethanol below 0.05%, which in itself has no effect on the microvascular parameters studied.

Drugs and chemicals

Leukotriene B_4 (LTB_4) was kindly provided by Dr J. Rokach (Merck-Frosst, Pointe Claire, PQ, Canada), and PGE_2, PGI_2, PGD_2, $PGF_{2\alpha}$ and U-44069 by Dr J. Pike (Upjohn, Kalamazoo, MI, U.S.A.). Arachidonic acid was from Nu-Chek Prep (Elysian, MN, U.S.A.). Stock solutions of arachidonic acid, LTB_4, PGE_2, PGD_2, $PGF_{2\alpha}$ and U-44069 were stored at −20°C in ethanol, and PGI_2 was made freshly for each experiment in a 10^{-2} M bicarbonate solution.

Acetylcholine chloride, fluorescein isothiocyanate-conjugated dextran (FITC-dextran, M_r 150,000), histamine dihydrochloride, pyrilamine maleate (mepyramine), and ovalbumin (grade III) were purchased from Sigma. Forskolin (stock solution in ethanol) was from Hoechst (Sweden), nitroprusside from Roche (Basel, Switzerland), and aluminium hydroxide ($Al(OH)_3$, dried gel, F2200) from Reheis (Kankakee, IL, U.S.A.).

Statistical analysis

Statistical evaluations were performed using the Mann-Whitney U-test. Data are expressed as mean values ± s.d.

Results

Effects of prostaglandins, forskolin, and nitroprusside on arteriolar tone and blood flow

Arachidonic acid, PGE_2 and PGI_2 caused dose-dependent arteriolar dilatation when added topically to the cheek pouch, whereas PGD_2 and $PGF_{2\alpha}$ failed to affect vessel diameters in concentrations up to 1 μM (Figure 1). The TXA_2 analogue U-44069 (10–100 nM), on the other hand, evoked arteriolar constriction as well as some platelet aggregation (not shown). The threshold concentrations for PGE_2 and PGI_2 were between 1 and 3 nM, and at 30 nM they caused ≈ 110% increase in arteriolar diameter and enhanced blood flow by 558% and 476%, respectively (Figure 2).

Forskolin and nitroprusside also caused dose-dependent arteriolar dilatation (Figure 1), and at a dose of 300 nM the arteriolar dilatation and increased blood flow induced by these two agents were of a magnitude similar to that caused by 30 nM PGE_2 or PGI_2 (Figure 1 and 2).

Microvascular responses to antigen challenge

As previously described (Raud *et al.*, 1988; 1989a), challenge of the hamster cheek pouch with antigen (ovalbumin,

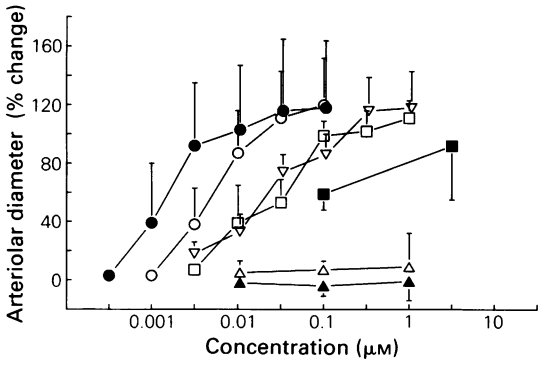

Figure 1 Changes of arteriolar diameters after topical challenge with prostaglandin E_2 (PGE_2, ○), PGI_2 (●), forskolin (▽), nitroprusside (□), PGD_2 (△), $PGF_{2\alpha}$ (▲), and arachidonic acid (■) in hamster cheek pouches. Data obtained by cumulatively increasing the dose of the vasodilators at 5 min intervals. The maximal change in vessel diameters relative to the control period was determined at the end of each 5 min challenge. Mean values with s.d. shown by vertical bars, *n* (number of animals) = 3–6 (one vessel per animal).

$10\,\mu g\,ml^{-1}$ topically for 5 min) evoked a brief vasospasm, followed by extensive leakage of plasma (i.e. FITC-dextran extravasation) (Figure 3a) and arteriolar dilatation (Figure 3b). Moreover, beginning 5–10 min after the start of challenge, there was a marked and long-lasting increase in the number of endothelium-adherent leukocytes, while few leukocytes emigrated to the extravascular interstitium during the 45 min observation time.

Effects of PGE_2 PGI_2, forskolin and nitroprusside on antigen-induced microvascular responses

When the 5 min antigen challenge was performed in the presence of PGE_2, PGI_2 or forskolin in equiactive vasodilator concentrations (topically for 15 min, starting 5 min before antigen), the plasma leakage responses were significantly reduced (Figure 3a and Figure 4). In these concentrations (30 nM of PGE_2 and PGI_2, and 300 nM of forskolin) the vasodilators *per se* caused virtually no increase in plasma extravasation (Figure 3a) and they appeared to be without effect on basal leukocyte-endothelium interactions.

The inhibitory activities of PGE_2, PGI_2 and forskolin on the antigen reaction seemed unrelated to vasodilatation, because nitroprusside (300 nM), which had very similar effects on arteriolar diameter, blood flow and basal microvascular parameters, enhanced the plasma leakage evoked by antigen (Figures 3 and 4). This despite the duration of nitroprusside-induced vasodilatation being shorter than that of PGE_2 or forskolin ($P < 0.05$ at 12.5 and 17.5 min) (Figure 3b).

Furthermore, while nitroprusside also strikingly potentiated the antigen-induced increase in leukocyte emigration, PGE_2, PGI_2, and forskolin were inactive in this respect (Figure 5).

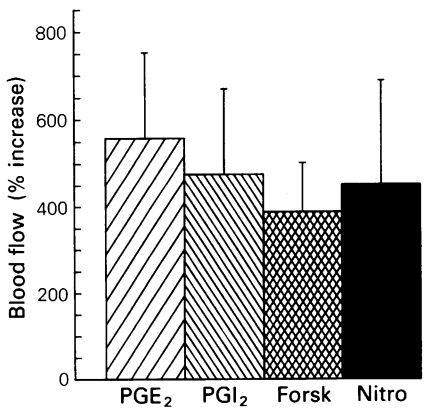

Figure 2 Effects of prostaglandin E_2 (PGE_2, 30 nM, $n = 6$), PGI_2 (30 nM, $n = 4$), forskolin (Forsk, 300 nM, $n = 4$), and nitroprusside (Nitro, 300 nM, $n = 4$) on arteriolar blood flow in hamster cheek pouches. Mean values with s.d. shown by vertical bars; *n* refers to number of animals (one vessel per animal).

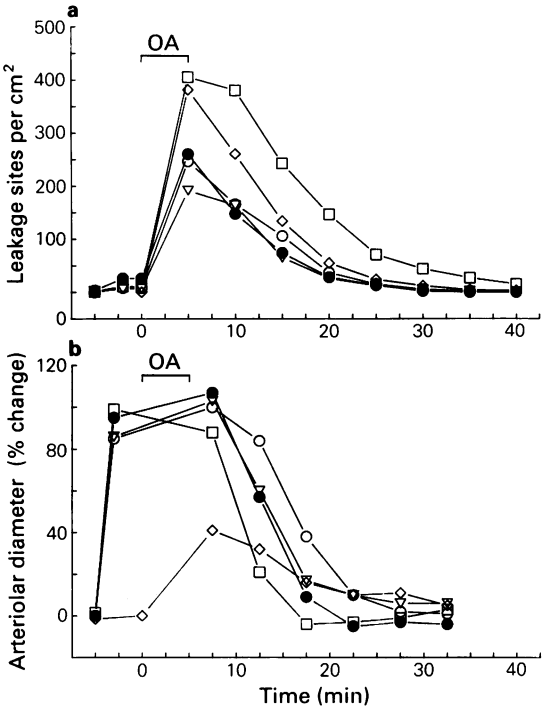

Figure 3 (a) Time course for plasma leakage (FITC-dextran leakage sites) in hamster cheek pouch after topical challenge with antigen (ovalbumin, OA) alone (control, $10\,\mu g\,ml^{-1}$ for 5 min, $n = 10$, ◇), and in the presence of prostaglandin E_2 (PGE_2, 30 nM, $n = 5$, ○), PGI_2 (30 nM, $n = 5$, ●), forskolin (300 nM, $n = 5$, ▽) or nitroprusside (300 nM, $n = 5$, □). (b) Changes in arteriolar diameters after antigen challenge (same experiments as in (a)). Vasodilators were given topically for 15 min, starting 5 min before antigen challenge. Mean values (error bars omitted for clarity); *n* refers to number of animals.

Effects of PGE_2, PGI_2, forskolin, and nitroprusside on histamine-induced microvascular responses

The antigen-induced plasma leakage was predominantly mediated by histamine, as indicated by experiments where

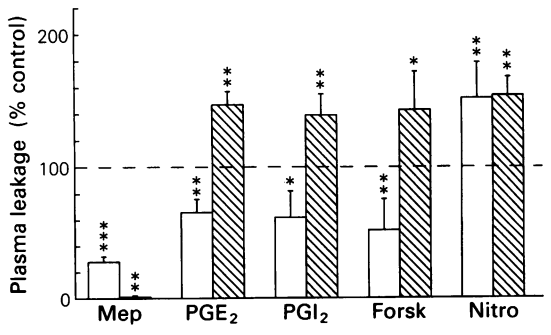

Figure 4 Total (0–40 min) leakage of plasma in hamster cheek pouch after topical challenge with antigen ($10\,\mu g\,ml^{-1}$, open columns) or histamine (10 μM, hatched columns) for 5 min. Effects (in % of control, dashed line, $n = 8$–10) of topically applied mepyramine (Mep, 1 μM, $n = 4$), prostaglandin E_2 (PGE_2, 30 nM, $n = 5$), PGI_2 (30 nM, $n = 5$), forskolin (Forsk, 300 nM, $n = 5$), and nitroprusside (Nitro, 300 nM, $n = 4$–5). Data with antigen ± vasodilators same as in Figure 3a. Mean values with s.d. shown by vertical bar * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$ vs. control. *n* refers to number of animals.

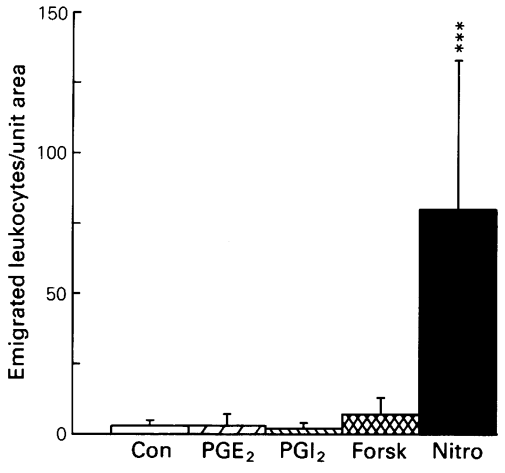

Figure 5 Increase in number of emigrated leukocytes in hamster cheek pouch 40 min after topical challenge with antigen alone (Con, 10 $\mu g\,ml^{-1}$ for 5 min, $n = 10$), and in the presence of prostaglandin E_2 (PGE_2, 30 nM, $n = 5$), PGI_2 (30 nM, $n = 5$), forskolin (Forsk, 300 nM, $n = 5$) or nitroprusside (Nitro, 300 nM, $n = 5$). Mean values with s.d. shown by vertical bars. *** = $P < 0.001$ vs. control. n refers to number of animals.

sensitized animals were pretreated with the H_1-receptor antagonist mepyramine (1 μM topically) (Figure 4). Therefore, it was of interest to examine whether PGE_2, PGI_2 and forskolin also could suppress histamine-induced plasma leakage. However, in contrast to the antigen response, these vasodilators enhanced the plasma leakage evoked by exogeneous histamine, and the same applied to nitroprusside (Figure 4). It should be noted in this context that the total (0–40 min) leakage of plasma after the dose of histamine used here (10 μM) was of similar magnitude to that induced by antigen (cf. Raud *et al.*, 1989a).

Effects of PGI_2 on LTB_4-induced microvascular responses

Recently, we showed that PGE_2 (30 nM topically) potentiates the leukocyte emigration and subsequent plasma leakage induced by the chemoattractant LTB_4 (Raud *et al.*, 1988). In the present study it was found that PGI_2 has a similar amplifying effect on LTB_4-induced inflammation in the cheek pouch. Thus, the total (0–40 min) plasma leakage response to LTB_4 (300 nM) in the presence of PGI_2 (30 nM, $n = 3$) was $192 \pm 61\%$ greater ($P < 0.05$) than that after LTB_4 alone ($n = 5$). In addition, the leukocyte emigration increased from 45 ± 37 emigrated leukocytes/unit area after LTB_4 alone (300 nM, $n = 5$), to 237 ± 112 in the presence of PGI_2 (30 nM, $n = 3$, $P < 0.05$).

Discussion

The present results confirm our previous observation that antigen-induced plasma extravasation in the hamster cheek pouch is suppressed by locally applied PGE_2 in a vasodilator concentration (Raud *et al.*, 1988). Because the antigen reaction is potentiated by pretreatment with indomethacin and appears to involve release of vasodilator prostaglandins (Raud *et al.*, 1988), it was of interest to examine if other vasodilator cyclo-oxygenase products exerted anti-inflammatory effects similar to those of PGE_2.

The initial characterization of the microvascular responses evoked by the major endogenous cyclo-oxygenase products revealed that only PGI_2 mimicked the vasodilator actions of PGE_2 in the cheek pouch, whereas PGD_2 or $PGF_{2\alpha}$ were inactive in this respect, and the TXA_2-analogue U-44069 caused vasoconstriction. Therefore, antigen challenge was performed in the presence of PGI_2 in a dose selected to cause vasodilatation equal to PGE_2. The results showed that PGI_2 and PGE_2 both reduced the antigen-induced plasma extravasation and to approximately the same extent.

Because PGE_2 or PGI_2 caused a close to maximal arteriolar dilatation and greatly increased local blood flow, it could be speculated that changes in microvascular haemodynamics were involved in the suppression of the antigen-induced plasma extravasation. However, when local blood flow in the cheek pouch was increased to the same degree with the potent vasodilator nitroprusside, the antigen-induced plasma leakage was instead potentiated. Moreover, PGE_2, PGI_2, and nitroprusside uniformly potentiated the plasma leakage evoked by challenge with exogenous histamine. The latter observation confirms our previous findings with PGE_2 (Raud *et al.*, 1988) and is in harmony with data reported for PGE_2 and PGI_2 by others (Williams & Morley, 1973; Komoriya *et al.*, 1978; Morley *et al.*, 1981, Rampart & Williams, 1986). Because histamine was a major mediator of the plasma extravasation evoked by antigen challenge (see Figure 4), it may be concluded that PGE_2 and PGI_2 did not inhibit the antigen response at the target site for histamine, i.e. the venules where the plasma extravasation occurs. Rather, the findings indicate that PGE_2 and PGI_2 inhibited the antigen response by suppression of histamine release. This is further supported by a previous study showing that PGE_2 indeed inhibits antigen-induced *in vivo* release of histamine in this particular model (Raud *et al.*, 1988). In addition, as indicated in the introduction, there are several *in vitro* studies documenting such a mode of action of PGE_2 and PGI_2. In this context, it is worth considering that the prostaglandins probably also suppressed antigen-induced release of chemotactic mediators. This interpretation is based on the following findings: (1) Prostaglandin E_2 and PGI_2 did not enhance the antigen-induced leukocyte activation, although they strikingly enhanced leukocyte emigration and subsequent plasma leakage evoked by LTB_4 (Raud *et al.*, 1988; this paper). (2) We have previously shown in the hamster cheek pouch that PGE_2 effectively inhibits the enhanced antigen-induced leukocyte emigration after pretreatment with indomethacin (Raud *et al.*, 1988). Because the potentiated leukocyte emigration is inhibited by 5-lipoxygenase inhibitors (Raud, 1989), it seems likely that this prostaglandin-sensitive response is mediated by LTB_4, or some other chemotactic 5-lipoxygenase product. (3) The leukocyte emigration after antigen challenge was markedly enhanced in the presence of nitroprusside-induced vasodilatation. Moreover, *in vitro* studies have shown that PGE_2 and PGI_2 can inhibit the release of chemotactic mediators from activated leukocytes (Camussi *et al.*, 1981; Ham *et al.*, 1983) and macrophages (Elliott *et al.*, 1989).

While the proinflammatory effects of vasodilator prostaglandins (i.e. PGEs and PGI_2) *in vivo* are generally attributed to increased microvascular blood flow and hydrostatic pressure (see Williams, 1983), it is suggested that cyclic AMP may act as the second messenger for the inhibition of inflammatory mediator release by these prostaglandins *in vitro* (Lichtenstein & Bourne, 1971; Kaliner & Austen, 1974; Weissmann *et al.*, 1980; Ham *et al.*, 1983; Peachell *et al.*, 1988). To gain some information as to whether the apparent link between cyclic AMP and suppression of mediator release by prostaglandins also exists *in vivo*, we added histamine or antigen to the cheek pouch in the presence of the diterpene derivative forskolin which is known to stimulate cyclic AMP production by a selective action on adenylate cyclase (Seamon *et al.*, 1981; Green & Clark, 1982). It was found that forskolin, in a dose causing equal increase in blood flow to PGE_2 and PGI_2, imitated the actions of the prostaglandins, i.e. the effect of antigen was inhibited while the histamine response was enhanced. Supported by previous observations that forskolin potentiates histamine-induced oedema formation (Sugio & Daly, 1983), and *in vitro* data that forskolin can inhibit anaphylactic release of histamine and leukotrienes from mast cells (Marone *et al.*, 1987; Peachell *et al.*, 1988), our results suggest that for-

skolin suppressed the antigen response by inhibiting mediator secretion. Although circumstantial, the forskolin data also indicate that the anti-inflammatory action of PGE_2 and PGI_2 may have been a consequence of cyclic AMP elevation. This notion gains further support by the failure of nitroprusside to suppress the antigen reaction, because nitroprusside stimulates the production of cyclic GMP rather than cyclic AMP (Rapoport & Murad, 1983).

Although most studies showing oedema potentiating effects of vasodilator prostaglandins *in vivo* have focused on microvascular target effects of exogenously applied directly acting inflammatory mediators, Williams & Morley (1973) and Williams *et al.* (1986) showed that locally applied PGE_1 also may enhance immunologically induced reactions in rabbit skin, dependent on endogenous inflammatory mediator release. This may seem in contrast to our findings; however, it could also illustrate that suppression of inflammatory mediator release by prostaglandins can be camouflaged by their proinflammatory vasodilator activities. It is possible that this interpretation is further reflected in a report by Morley *et al.* (1981), who showed in guinea-pig skin that local PGE_2 potentiated the plasma extravasation induced by various exogeneous mediators, including histamine and leukotrienes, but failed to affect immunologically triggered inflammation which was found to be dependent on endogenous release of histamine and leukotrienes. Accordingly, Komoriya *et al.* (1978) showed in rat skin, that PGE_1 and PGI_2 enhanced the increase in permeability evoked by histamine, but not that caused by adenosine 5'-triphosphate (ATP) which is known to cause mast cell degranulation (Kiernan, 1972) and histamine release (Diamant & Krüger, 1967). In analogy, Sugio & Daly (1983) reported that forskolin greatly enhanced histamine-induced plasma extravasation in rat skin, whereas corresponding skin reactions to 1 μg PGE_1 were reduced by forskolin. Interestingly, plasma extravasation in rat skin to such high doses of PGE_1 has been shown to involve histamine release (Crunkhorn & Willis, 1971).

These seemingly discordant observations regarding the influence of vasodilator prostaglandins on inflammatory responses involving release of endogenous mediators may be reconciled if results in different models are considered with respect to the degree of basal blood flow in each particular system. Thus, in tissues with low basal blood flow, PGE_2 and PGI_2 would be more prone to enhance inflammation as a result of mediator synergism. On the other hand, in a system with high blood flow, it is likely that inhibition of mediator release will be the most obvious action of these prostaglandins. Such an interpretation would explain the different actions of PGEs on immunologically evoked inflammation in the skin of guinea-pigs and rabbits, and in the hamster cheek pouch. Specifically, in the hamster cheek pouch, which is well perfused, the data with PGE_2 and PGI_2 strongly indicate that inhibition of mediator release predominates over mediator synergism. In contrast, in the rabbit skin, which is likely to have a relatively lower basal blood flow, the dominant effect of PGE_2 will be enhancement of inflammation due to vasodilator synergism with released mediators. That the hamster cheek pouch model and the rabbit skin model are different is for example illustrated by comparing the action of LTB_4 in the two systems. Thus, while LTB_4 itself effectively promotes plasma leakage in the hamster cheek pouch (Björk *et al.*, 1982), it can only induce oedema in the rabbit skin in the presence of a vasodilator such as PGE_2 (Bray *et al.*, 1981). It seems feasible that these differences to a large extent relate to variations in basal blood flow between the two models.

Taken together, the present observations indicate that vasodilatation and inhibition of mediator release are two distinct actions of PGE_2 and PGI_2 which modulate inflammatory reactions involving release of endogenous mediators. As discussed in detail above, the final outcome of these opposite actions of vasodilator prostanoids is likely to vary with different species, tissues and inflammatory reactions. Accordingly, such a dual prostaglandin action may contribute to the understanding of variable results in studies where NSAIDs or prostaglandins are used to modify different types of inflammation.

Supported by grants from the Knut and Alice Wallenberg Foundation, the Swedish Medical Research Council (14X-4342, 14X-09071, 04P-8865), the Institute of Environmental Medicine, the National Environment Protection Board (5324068-5), the Swedish Society for Medical Research, King Gustav V's Research Foundation, and Karolinska Institutet.

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(Received April 7, 1989
Revised August 8, 1989
Accepted November 8, 1989)