PROSTAGLANDIN I_2 AS A POTENTIATOR OF ACUTE INFLAMMATION IN RATS

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Abstract

Prostaglandin I_2 potentiated the paw swelling induced by carrageenin in rats. Prostaglandin I_2 (0.1 μg) showed similar activity to PGE_1 (0.01 μg). This potentiating property disappeared in 60 minutes and was completely abolished by diphenhydramine (25 mg kg^{-1}, i.p.). In vascular permeability tests, PGI_2 itself (2.5×10^{-10} mol, 88 ng) caused no dye leakage reaction, but PGE_1 (2.5×10^{-10} mol, 88.5 ng) caused a significant dye leakage. This effect of PGE_1 was statistically significant compared with vehicle- or PGI_2-treated groups ($p<0.05$). Prostaglandin I_2 potentiated the increased vascular permeability induced by 5-hydroxytriptamine (2.5×10^{-10} mol), bradykinin (5×10^{-10} mol) and histamine (2×10^{-10} to 2×10^{-8} mol). The potentiation was the most evident in the case of histamine.

Key words: PGI_2, PGE_1, carrageenin oedema, vascular permeability, histamine.

PROSTAGLANDINS

Introduction

Prostaglandins of E series (i.e. PGE_1 and PGE_2) are released in inflammatory lesions (1-3) and produce or enhance such inflammatory signs as increased vascular permeability (4-7), pain (8,9), fever (10) and bone resorption (11). In an animal model of inflammation, PGEs potentiate oedema formation or increased vascular permeability induced by carrageenin, dextran, histamine, substance P or bradykinin (4-7).

Prostaglandin E_1 has an inhibitory effect on platelet aggregation (12). Intensive studies on the metabolism of arachidonic acid have recently proved that PGI_2 (prostacyclin, PGX) is a more potent inhibitor of platelet aggregation and relaxes coeliac and mesenteric arteries (13,14). The catabolite of PGI_2, 6-keto $PGF_{1\alpha}$, has recently been detected in carrageenin induced granuloma (15) or in macrophages challenged by inflammatory stimuli (16). A PGI_2-like substance is produced by 3T3 fibroblasts (17). However, it remains to be elucidated whether PGI_2 participates in inflammation.

In the present paper, we studied the effect of PGI_2 on acute inflammatory processes in comparison with that of PGE_1.

Methods

Male rats, Sprague-Dawley strain, weighing 150-200 g, were used in all experiments.

Carrageenin induced foot-oedema

Carrageenin (1 %w/v, 0.1 ml) was injected into the hind paw to induce inflammation (18). Some rats received a mixture of carrageenin and either PGI_2 or PGE_1 (0.01 and 0.1 μg). The foot volume was measured by the water displacement method (19) and the result was expressed as the increased per cent of foot volume.

When effects of anti-inflammatory agents were tested, drugs were administered intraperitoneally 30 minutes before carrageenin injection.

Vascular permeability test

Under light ether-anaesthesia, intradermal injections of prostaglandin (PGI_2 or PGE_1) alone or by mixing with 5-hydroxytriptamine (5HT), histamine, bradykinin or ATP were given into separate region of the shaved abdominal skin in 0.1 ml volumes. Immediately, evans blue (25 mg kg^{-1}, 2 ml kg^{-1} in saline) was injected into a lateral tail vein. Thirty minutes later, animals were killed and the extent of the dye leakage was measured spectrophotometrically according to the method of Harada *et al.* (20).

Phlogistic agents and prostaglandins were diluted in phosphate buffer (25 mM, pH 7.2).

Results and Discussion

Carrageenin induced foot-oedema

Fig. 1 shows the potentiation by PGI_2 or PGE_1 of the rat paw swelling induced by carrageenin. Prostaglandin I_2 and PGE_1 (0.01 and 0.1 μg) potentiated the paw swelling at 20 minutes, in a dose dependent manner. At 0.1 μg dosage, PGI_2 showed similar activity to PGE_1 (0.01 μg), however, these potentiating effects disappeared in 60 minutes. These prostaglandins did not cause significant oedema by themselves. The potentiation was also observed when PGI_2 was injected into the paw at 20 to 80 minutes after carrageenin injection.

The potentiating effects of PGI_2 were completely inhibited by the anti-histaminic, diphenhydramine (25 mg kg^{-1}), but steroidal or non-steroidal anti-inflammatory drugs such as dexamethasone (2 mg kg^{-1}) or indomethacin (10 mg kg^{-1}), showed no inhibition, as shown in Fig. 2. The similar results were obtained in the potentiating effects of PGE_1 (data not shown).

These results suggest that PGI_2 might be involved in the histamine induced inflammatory responses by potentiating the effects of histamine.

Vascular permeability test

We investigated whether PGI_2 potentiates increased vascular permeability induced by mediators which are involved in the initial phase of the inflammatory process.

Prostaglandin I_2 alone (2.5×10^{-10} mol, 88 ng) caused no significant dye leakage (OD at 620 nm : 0.088±0.013) compared with vehicle (0.094±0.009), but PGE_1 caused a significant dye leakage (0.136±0.016) compared with vehicle ($p<0.05$). This effect of PGE_1 was statistically significant compared with vehicle- or PGI_2-treated group ($p<0.05$). At this concentration, PGI_2 exerted a synergistic effect on the increased vascular permeability induced by histamine (2×10^{-8} mol), and potentiated the dye leakage action of 5HT (2.5×10^{-10} mol), bradykinin (5×10^{-10} mol) or ATP (10^{-7} mol) to a lesser extent. These latter effects were not statistically significant (Fig. 3). Similar results were obtained with PGE_1. Under the experimental conditions, however, the potentiating effects of PGE_1 were additive rather than synergistic in the case of bradykinin or 5HT. Adenosine-5'-triphosphate (10^{-7} mol) as well as histamine (2×10^{-8} mol) produced a similar dye leakage. Adenosine-5'-triphosphate is considered to cause dye leakage by releasing histamine (21). As shown in Fig. 3, PGE_1 and PGI_2, however, had no significant potentiating effect on ATP induced dye leakage in contrast to the case of histamine. This may be explained by the fact that PGE_1 inhibits ATP-induced histamine release from mast cells (22). The same might apply for PGI_2.

Prostaglandin I_2 or PGE_1 (2.5×10^{-11} to 2.5×10^{-10} mol) potentiated and histamine (2×10^{-10} to $2\ 10^{-8}$ mol)-induced dye leakage, particularly when the higher concentrations of histamine were used,

as shown in Fig. 4.

Prostaglandin I_2 is easily degraded to 6-keto $PGF_{1\alpha}$ by heat treatment (13). The effect of PGI_2 on the potentiation of carrageenin-induced oedema and of histamine-induced dye leakage was completely abolished by heat treatment. This result indicated that the effect was due to PGI_2 itself.

These results suggest that PGI_2 might be involved in the inflammatory response by potentiating the effect of histamine.

In conclusion, PGI_2 potentiates carrageenin induced foot-oedema and the increased vascular permeability induced by histamine. The results obtained in experimental inflammations imply that PGI_2 may have some physiological significance in the inflammatory processes.

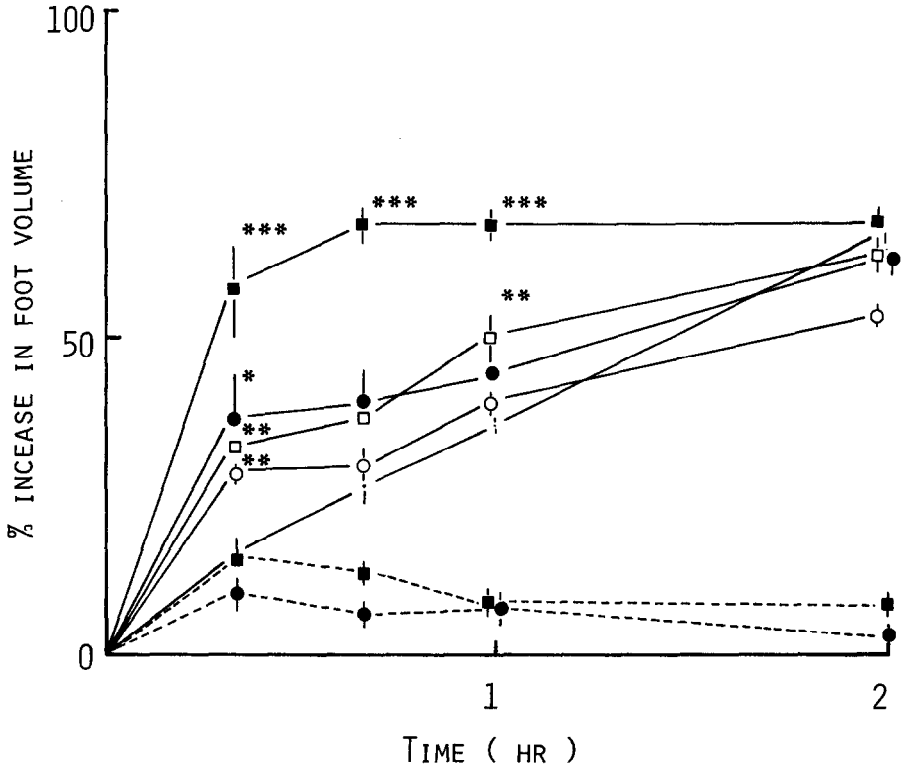

Fig. 1. Potentiation by PGI_2 or PGE_1 of the rat paw swelling induced by carrageenin.
Carrageenin (C, 1 %w/v, 0.1 ml, —·—), C+PGI_2 (0.01 µg, —○—), C+PGI_2 (0.1 µg, —●—), C+PGE_1 (0.01 µg, —□—), C+PGE_1 (0.1 µg, —■—), PGI_2 (0.1 µg, ----●----), and PGE_1 (0.1 µg, ----■----). Each point is the mean ± s.e.m. of a group of 5 rats. Significant difference from control ; * ($p<0.05$), ** ($p<0.01$) or *** ($p<0.001$).

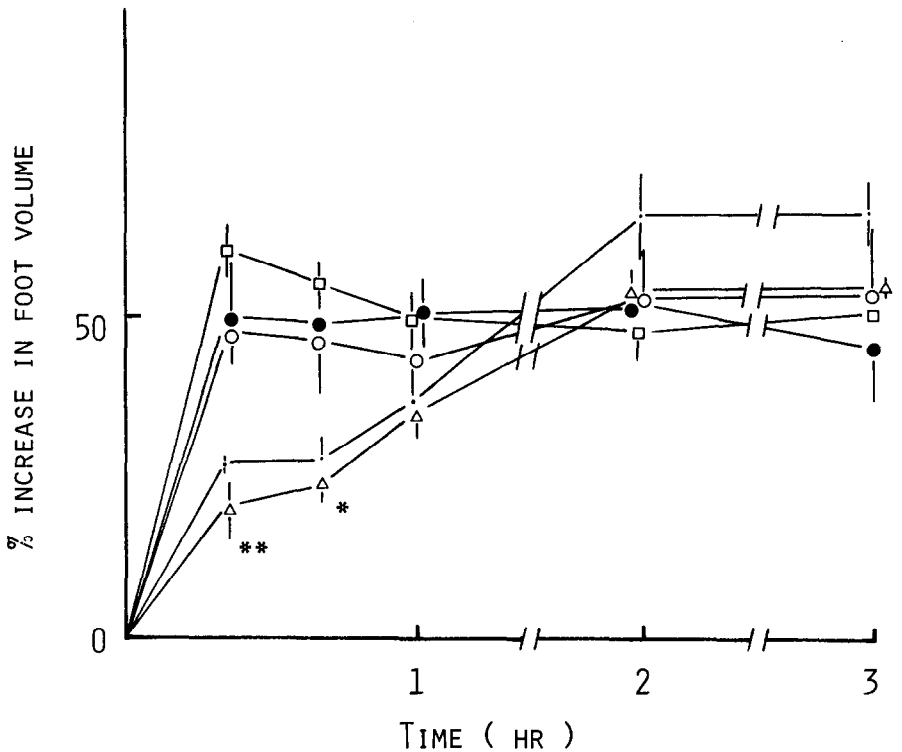

Fig. 2. Effect of anti-inflammatory drugs on the potentiation of carrageenin induced foot oedema by PGI_2.
0.1 ml of 1 % carrageenin (C) containing 0.1 µg of PGI_2 was injected into the hind paw of rats. In some cases, indicated anti-inflammatory drugs were administered intraperitoneally 30 minutes before carrageenin injection. C (—·—), C+PGI_2 (—○—), C+PGI_2+indomethacin 10 mg kg^{-1} (—□—), C+PGI_2+dexamethasone 2 mg kg^{-1} (—●—), and C+PGI_2+diphenhydramine 25 mg kg^{-1} (—△—). Each point is the mean ± s.e.m. of a group of 5 rats. Significant difference from carrageenin plus PGI_2 treated group (*, $p<0.05$ or **, $p<0.01$).

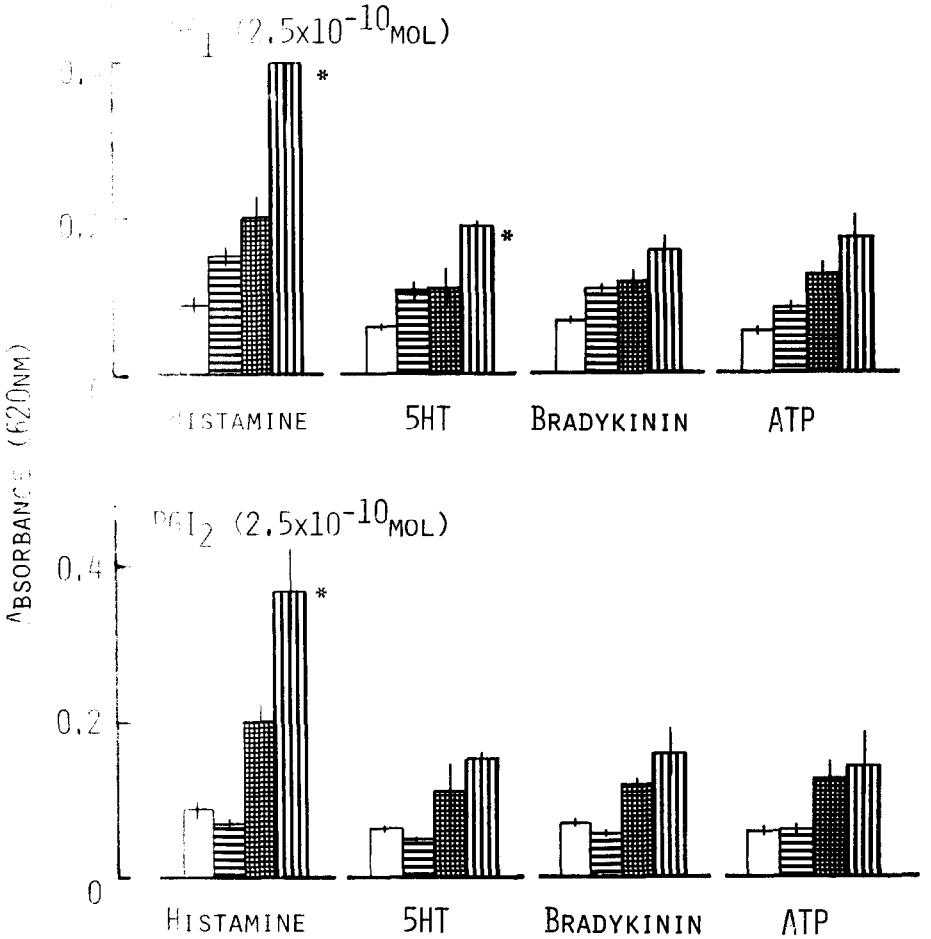

Fig. 3. Potentiation by PGI_2 or PGE_1 of increased vascular permeability induced by histamine ($2x10^{-8}$mol), 5-hydroxytriptamine (5HT, $2.5x10^{-10}$mol), bradykinin ($5x10^{-10}$mol) or ATP (10^{-7}mol). □, vehicle only ; ▤, PGI_2 or PGE_1 ; ▦, mediator ; ▥, PG+mediator. Each value represents the mean ± s.e.m. of a group of 5 rats. Significant difference from mediator treated group ; * ($p<0.05$)

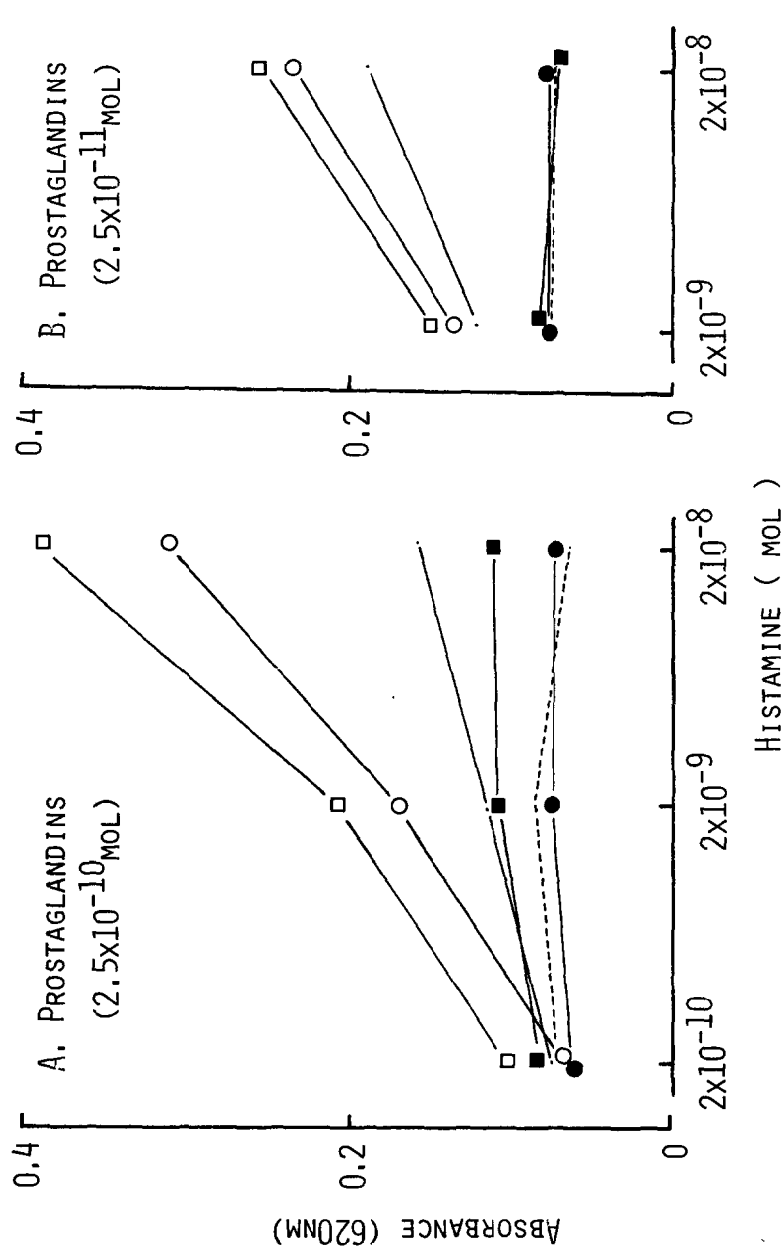

Fig. 4. Potentiation by PGI_2 or PGE_1 of increased vascular permeability induced by histamine. A. PGI_2 or PGE_1 ($2.5x10^{-10}$mol). B. PGI_2 or PGE_1 ($2.5x10^{-11}$mol). Histamine (H), —□—; $TxPGI_2$, —○—; PGI_2, —□—; PGE_1, —●—; vehicle only, ----. Each point is the mean of 5 rats.

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