Oedema and vasodilatation in inflammation: the relevance of prostaglandins

T. J. WILLIAMS
B.Sc.

Department of Pharmacology, Institute of Basic Medical Sciences, Royal College of Surgeons of England

Summary

The role of prostaglandins in inflammation is still disputed. Some workers have attempted to fit prostaglandins into a simple model, i.e. inflammatory cell → chemical mediator → vascular response. Recent work has shown that this approach may be misleading. An alternative model is proposed, involving the interaction of two chemical agents, i.e. a vascular permeability-increasing mediator (such as histamine or bradykinin) and a vasodilator (prostaglandin) which potentiates the plasma exudation produced by the permeability-increasing mediator. The results obtained in testing this model support the further proposal that non-steroidal anti-inflammatory compounds suppress inflammatory swelling by inhibiting vasodilatation.

Introduction

Since the discovery of prostaglandins in inflammatory exudate (Willis, 1969), and that non-steroidal anti-inflammatory compounds inhibit the synthesis of prostaglandins (Vane, 1971), the mode of action of prostaglandins has been extensively investigated. The observation that injection of prostaglandins into the skin of the guinea-pig and rabbit produces little plasma exudation (Williams and Morley, 1973; Williams, 1976a) is not consistent with a simple mediator concept as has previously been proposed for substances such as histamine and bradykinin. It was found, however, that in guinea-pig skin, prostaglandins were able to potentiate the exudation produced by vascular permeability-increasing mediators (Williams and Morley, 1973). A similar phenomenon was observed in other species (Moncada, Ferreira and Vane, 1973; Thomas and West, 1973).

It was suggested (Williams and Morley, 1973) that prostaglandins may exert their potentiating effect because of their potent vasodilator activity. This hypothesis has been tested using a technique developed to measure plasma exudation and changes in blood flow simultaneously in animal skin (Williams, 1976b). The results of this study suggest a

role for prostaglandins in inflammation, and provide an explanation for the mode of action of non-steroidal anti-inflammatory compounds in terms of microvascular changes.

Methods

Rabbits (New Zealand White, male, 3.5-4.5 kg) received an intravenous injection of methohexitone sodium (10 mg/kg) followed by intravenous ^{131}I -human serum albumin. Multiple injections (36-72) of inflammatory test substances mixed with ^{133}Xe were then given into the dorsal skin (previously clipped). Injections were given in random block order according to a balanced site pattern, with six replicates for each dose. After a predetermined interval (20 or 30 min), the animal was killed, the skin removed, and the injection areas excised with a steel punch (16 mm diameter). The skin samples were placed in paraffin oil in sealed tubes and counted, together with blood samples and injection fluid samples, in an automatic γ -counter. Results were computed from punched tape using a PDP-12 computer. Plasma exudation was computed from ^{131}I accumulation, and local blood flow changes from ^{133}Xe clearance, as previously described (Williams, 1976b).

Results

Figure 1 demonstrates that intradermal injection of PGE_2 produced a dose-related increase in local blood flow with little evidence of exudation. Figure 2 shows that increasing doses of PGE_2 added to a fixed dose of histamine resulted in a marked potentiation of the histamine-induced exudation.

The evidence linking exudation-potential with vasodilatation has been previously described (Williams, 1976a). The rank order of potency of different prostaglandins was the same for potentiating and vasodilating activity, i.e. $\text{PGE} > \text{PGA} > \text{PGF} > \text{PGD}$. Other substances which produced an increase in blood flow (although much less potent than prostaglandins), e.g. isoprenaline, adenosine and adenosine diphosphate, also potentiated responses to histamine. Conversely, substances which reduced

FIG. 1. Dose-response curve to PGE₂ in rabbit skin. Top trace shows that increasing doses of PGE₂ (in 100 μ l injections) produced little evidence of exudation, as measured by ¹²⁵I-albumin accumulation. Dotted line represents plasma volume in saline-injected control sites. Lower trace shows increasing blood flow in response to increasing doses of PGE₂, as measured by ¹³³Xe clearance. Blood flow is expressed as percentage of flow in saline-injected sites. (Results are expressed as: mean $\pm$ s.e. mean, $n=6$.)

blood flow, e.g. noradrenaline and angiotensin II, reduced responses to histamine. These results strongly suggest that the potentiation of exudation produced by prostaglandins is a result of their vasodilator activity, perhaps as a consequence of increased vessel wall area.

These observations using exogenous agents have been extended to investigate the interaction between permeability-increasing mediators and vasodilator agents in inflammatory reactions produced by injection of foreign materials (Williams, 1977). Intradermal injection of *Bordetella pertussis* (2.5×10^8 organisms/site) resulted in an increase in blood flow and a small exudation response with a peak at 60–90 min. If the observed exudation resulted from the interaction described, then addition of either exogenous permeability-increasing agent (histamine or bradykinin) or vasodilator (PGE₁) should potentiate the response. Figure 3 shows that both of these criteria were fulfilled. This experiment is important because it enables one to locate the site of action of a non-steroid anti-inflammatory compound. The non-steroid anti-inflammatory compound, indomethacin, suppressed the potentiation produced by *B. pertussis* and exogenous bradykinin, but failed to suppress the potentiation produced by

FIG. 2. Potentiation of plasma exudation produced by a fixed dose of histamine (H) and increasing doses of PGE₂. (Results expressed as in Fig. 1.)

B. pertussis and exogenous PGE₁. This demonstrates that indomethacin suppressed the production of the endogenous potentiating agent (probably an E-type prostaglandin) without affecting the production of the endogenous (unidentified) permeability-increasing mediators.

Discussion

These results emphasize the importance of prostaglandins (especially PGEs) in inflammation. Their importance would appear to depend on their potent vasodilator activity; this results in a potentiating action on plasma exudation. Because of this phenomenon, concomitantly released permeability-increasing mediators may be present in low concentrations in inflammatory reactions.

In the inflammatory model used, indomethacin did not inhibit the production of permeability-increasing mediators. This is not consistent with the recently published hypothesis that the permeability-increasing mediator is a product of arachidonic acid metabolism, proposed to be PGG₂ or a free radical (Kuehl *et al.*, 1977). Further, the frequent observation that non-steroidal anti-inflammatory drugs inhibit mediator release *in vitro* (e.g. Trethewie, 1951;

FIG. 3. The effects of indomethacin on the exudation produced by intradermal injection of *Bordetella pertussis* (BP) in the presence of exogenous bradykinin (Bk, 0.5 μ g) or exogenous PGE₁ (0.5 μ g). Ordinate for both experiments is plasma volume in skin sites. Abscissa: top line is first intradermal injection; lower line is second intradermal injection into the same site 60 min later. Plasma exudation was measured for 30 min following the second injection. Dotted line represents plasma volume in sites given two saline injections, and dashes represent single saline injections. Note that indomethacin (Indo, mixed with *B. pertussis*) suppresses potentiation in *B. pertussis*/bradykinin sites but not the potentiation in *B. pertussis*/PGE₁ sites. (Results are expressed as in Fig. 1.)

Norn, 1971) did not seem to apply to the described *in vivo* experiments.

These conclusions require verification using other inflammatory test systems, but from the results described, it is proposed that non-steroidal anti-inflammatory compounds inhibit inflammatory exudation by suppressing vasodilatation.

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