We can see a good example of this when we examine acute pain. Both histamine and bradykinin produce pain when low concentrations are injected intradermally, whereas prostaglandins in similar concentrations cause no pain. If, on the other hand, histamine or bradykinin is injected at the same site as the prostaglandin the pain produced is greatly potentiated in intensity and duration. Tim Williams, a member of my department, is particularly interested in this interaction of prostaglandin with histamine and bradykinin with regard to their effect on vascular permeability. In this respect too, the prostaglandins potentiate the action of the other two mediators. It might well be, and this will be one of the points he will discuss, that this potentiation is the result of the vasodilatation produced by the prostaglandins. Even Hunter some 200 years ago pointed out that 'the colour [vasodilatation] and the swelling [increased permeability] correspond very much since they both depend on the same principle'.

There appears to be another kind of modulating effect exerted by prostaglandins which works in the opposite direction, resulting in an inhibitory effect. It has been shown, in the US as well as in this country, in isolated systems that some inflammatory cells have receptors which, when stimulated, cause an increase in intracellular cyclic adenosine monophosphate which in some way inhibits the release of mediators. It has also been shown that prostaglandins stimulate such a receptor and cause a reduction in the release of other mediators. Dr Priscilla Piper and her colleagues, also in the Department of Pharmacology, have shown this to occur in an immunological response in sensitised guineapig lungs. She will show later that when the prostaglandin system is greatly reduced by giving indomethacin, this reaction produces a great release of histamine and slow-reacting substance of anaphylaxis (SRS-A). This finding is a good illustration of the inhibition of a negative feedback mechanism. SRS-A is one of the acute mediators about which not very much is known, and Dr Piper is kindly going to bring us up to date on that particular subject.

In spite of all the research that has been carried out on the subject of inflammation since Hunter's *Treatise* of 1794 it is still a subject which 'requires our greatest attention'.

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THE ROLE OF PROSTAGLANDINS IN INFLAMMATION

T J Williams BSC

Department of Pharmacology, Royal College of Surgeons of England

Introduction

John Hunter was the first to recognise that the redness of inflammation was due to an increase in blood supply to the affected tissues and that tissue swelling was due to an extravasation of fluid from the blood[1]. A contemporary of Hunter, the Reverend Edmund Stone, discovered[2] that willow bark contained an active ingredient, later to be called aspirin. Two centuries passed before the evidence was obtained which linked these independent observations. Firstly, Willis[3] detected prostaglandins in inflammatory exudates, and secondly, Vane and his co-workers[4] discovered that aspirin inhibited the synthesis of prostaglandins in vitro. However, the reports concerning the exact mechanism of action of prostaglandins in inflammation have been as

confusing as they have been plentiful. This confusion has been exacerbated more recently by the discovery of further products of the prostaglandin synthesis system, some of them very active on certain tissues but unstable in aqueous solution.

Prostaglandin synthesis

An outline of present knowledge concerning prostaglandin (PG) synthesis is shown in Figure 1. Arachidonic acid, mobilised from cell membrane phospholipid, is converted by an enzyme system (cyclo-oxygenase) to unstable intermediate prostaglandin endoperoxides, PGG_2 and PGH_2. This conversion is inhibited by aspirin-like compounds. The endoperoxides can be converted enzymically or spontaneously to the stable prostaglandins, PGE_2, $PGF_{2\alpha}$ and PGD_2. Alternatively, the endoperoxides can be converted enzymically to thromboxane A_2 (TXA_2)[5], a potent platelet aggregator, or PGI_2[6], a potent inhibitor of platelet aggregation. These unstable substances spontaneously break down in aqueous solution to thromboxane B_2 and 6-oxo-$PGF_{1\alpha}$, respectively.

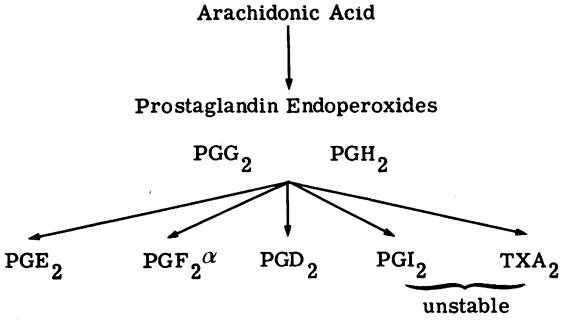

FIG. 1 *Prostaglandin synthesis.*

Prostaglandins and increased vascular permeability

Kaley and Weiner[7], from their studies in rat skin, proposed that PGEs mediated inflammatory swelling by increasing vascular permeability, although Crunkhorn and Willis[8] thought that PGEs acted indirectly by releasing mast cell amines.

Other prostaglandins have been implicated in inflammation; Willoughby *et al*[9] suggested that PGE_2 was pro-inflammatory and $PGF_{2\alpha}$ was anti-inflammatory. They reported that PGE_2 was high early in the inflammatory reaction and $PGF_{2\alpha}$ was high in the late stages, thus suggesting a control system. In another study Flower *et al*[10] suggested that an isomer of PGE_2, PGD_2, could be an important inflammatory mediator.

Prostaglandins and potentiation of plasma exudation

Our studies on guineapig[11] and rabbit skin[12], however, showed that when plasma exudation was measured quantitatively using radioisotopic techniques none of the prostaglandins produced significant plasma exudation when injected intradermally. A similar situation was reported in man, where intradermal injection of PGE_1 or PGE_2 produced erythema with little or no wealing[13]. In terms of inflammatory oedema we consider the importance of prostaglandins to be their ability to potentiate the plasma exudation induced by other mediators such as histamine and bradykinin. This was shown by us in the guineapig[11] and rabbit[12] and by Moncada *et al*[14] in the rat. Initially we thought that this striking phenomenon was analogous to the prostaglandin-induced hyperalgesia reported earlier[13, 15], which is probably due to sensitisation of receptors. We did, however, suggest[11] that prostaglandin-induced potentiation of plasma exudation may be a consequence of the potent vasodilator activity of certain prostaglandins.

In order to investigate this we devised a technique to measure both plasma exudation and changes in blood flow simultaneously in rabbit skin using intravenously-injected ^{131}I-albumin and locally injected ^{133}Xe[16]. The results of this study strongly suggested that the enhancement of plasma exudation induced by prostaglandins is a result of their vasodilator activity[17, 18].

The two-mediator hypothesis

A two-mediator hypothesis was postulated (see Figure 2) to account for these observations[17, 18]. It was proposed that inflammation involves the separate production of mediators which increase vascular permeability and mediators which increase local blood flow. This means that because of the phenomenon of exudation potentiation the amount of inflammatory swelling depends on the levels of both types

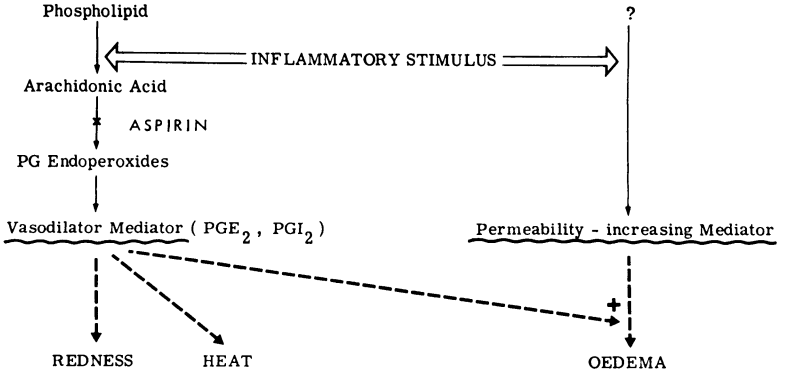

FIG. 2 *The two-mediator hypothesis.*

of mediator. The action of the endogenous permeability-increasing mediators can be mimicked by histamine and bradykinin (which have weak vasodilator activity), although the substances actually involved in mediating this part of the response remain unknown except in certain limited situations. The action of the endogenous vasodilators can be mimicked by certain of the prostaglandins, and much evidence exists to indicate that these substances are important in mediating vasodilatation in inflammation. PGD_2 and PGF_{2a} have only weak vasodilator activity[18] and are unlikely to be of importance.

Mechanism of action of aspirin-like compounds

The above hypothesis predicts that aspirin-like compounds act on the production of vasodilator mediators in inflammation. In support of this we found[18] that intradermal injection of either the prostaglandin precursor, arachidonic acid, or the prostaglandin endoperoxide, PGG_2, resulted in vasodilatation and potentiation of bradykinin-induced exudation. However, the effects of arachidonic acid were abolished by an aspirin-like compound, indomethacin, whereas the effects due to PGG_2 (like PGE_2) were unaffected. This is consistent with the in-vitro observation[4] that the aspirin-like compounds inhibit conversion of arachidonic acid to PGG_2 (that is, at the cyclo-oxygenase step).

We then demonstrated that intradermal injection of *Bordetella pertussis* in the rabbit resulted in the production of an endogenous permeability-increasing mediator (unidentified) and a vasodilator mediator (probably a prostaglandin). In this model system we showed that indomethacin acted specifically on the production of the vasodilator (exudation-potentiating mediator).

Thus it was postulated[18] that aspirin-like drugs inhibit inflammatory swelling as a consequence of an inhibition of vasodilatation.

Recent theories

Recently Kuehl *et al*[19] have revived the idea that increased vascular permeability is mediated by a product of prostaglandin synthesis. They have found that a compound which has no effect on cyclo-oxygenase activity in vitro but has free radical scavenging properties, also has anti-inflammatory activity in vivo. They propose that a free radical liberated when PGG_2 is converted to PGH_2 is responsible for increasing permeability.

This idea is difficult to test because of the very transient nature of the free radicals. However, it is significant that in our experiments intradermal injection of either arachidonic acid or PGG_2, both of which should liberate free radicals in vivo, produced vasodilatation with little evidence of an increase in vascular permeability[18].

Another hypothesis has been put forward by Moncada and Vane[20]. They have postulated that the unstable PGI_2 is produced normally, but in an inflammatory reaction synthesis is directed to PGE_2. Contrary to this idea we have reported[21] that PGI_2, when injected into rabbit skin, has similar characteristics to PGE_2—that is, potent vasodilator and exudation-potentiating activity. Further, indomethacin was found to have no effect on normal blood flow, suggesting that no detectable vasodilator prostaglandin is produced in normal conditions in our model. Thus a diversion from PGI_2 production to PGE_2 pro-

duction does not appear to be an a priori requirement in inflammation and both prostaglandins should be considered as possible inflammatory mediators[21].

Conclusions

These observations suggest that certain prostaglandins (PGE_2, PGI_2) are important in inflammation because of their vasodilator activity. Their vasodilator activity greatly potentiates the oedema produced by concomitantly generated vascular permeability-increasing mediators which are unidentified in most inflammatory reactions. Certain prostaglandins also have the important property of potentiating pain responses[15], which is probably due to a sensitisation of pain receptors.

Our work suggests that aspirin-like drugs suppress inflammatory oedema not by reducing vessel wall permeability but by inhibiting the production of vasodilator mediators (prostaglandins), which results in a reduction in plasma exudation. Thus aspirin-like drugs appear to inhibit inflammatory swelling in the same manner as the traditional method of cooling with an ice-pack—by constricting the dilated blood vessels.

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SLOW-REACTING SUBSTANCE OF ANAPHYLAXIS

Priscilla J Piper, BSC PHD

Department of Pharmacology, Royal College of Surgeons of England

Introduction

Slow-reacting substance of anaphylaxis (SRS-A) is a primary mediator of immediate-type hypersensitivity reactions and is released together with histamine and the other primary mediators. The term slow-reacting substance (SRS) was initially used to describe the biologically active non-histamine material released from lung tissue by cobra venom or antigen challenge[1, 2]. Brocklehurst[3] first characterised the material released during anaphylaxis and named it slow-reacting substance of anaphylaxis (SRS-A). Since this time various groups have attempted extensive characterisation of the physicochemical and biological properties of SRS-A and to elucidate its structure, but these studies have been hampered by the use of impure material and the structure of SRS-A is still unknown.

Release of SRS-A

SRS-A is released by antigen challenge of lung tissue from various species including man, guineapig, rhesus monkey, and cattle[3, 4] and also from cells in the rat peritoneal cavity[5] and human leucocytes[6]. In contrast to histamine,