Br. J. Pharmac. (1971), **41**, 507–512.

Interaction between prostaglandins E and F given intradermally in the rat

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Summary

1. Increases in permeability observed after intradermal injection of prostaglandins PGE_1 or PGE_2 (0·1 μg) into rats were greatly reduced when they were given in admixture with $PGF_{2\alpha}$. This effect was not seen with $PGF_{1\alpha}$ at doses of 0·5–1 μg.

2. Effects of the histamine releasing agent compound 48/80 (25 ng) were inhibited by $PGF_{2\alpha}$ (0·5 μg) but not by $PGF_{1\alpha}$ (0·5 μg).

3. Responses to histamine (1 μg), 5-hydroxytryptamine (0·1 μg) and bradykinin (1 μg), which have a direct action on the microvasculature, were not significantly altered by $PGF_{2\alpha}$ (0·5 μg).

4. It is concluded that $PGF_{2\alpha}$ probably acts by interfering with the release of mast cell histamine by PGE_1, PGE_2 and compound 48/80.

Introduction

Prostaglandin E_2 (PGE_2) has been identified in rat inflammatory exudate (Willis, 1969, 1971) and we (Crunkhorn & Willis, 1969, 1971) have recently found that intradermal PGE_1 and PGE_2 are potent inducers of local vascular permeability in the rat and man. In the rat the effects of PGE_1 and PGE_2 were apparently mediated via release of histamine and 5-hydroxytryptamine from skin mast cells; $PGF_{1\alpha}$ and $PGF_{2\alpha}$ caused little change in local vascular permeability even in doses of up to 1 μg. The present study examines whether these F-type prostaglandins enhance or inhibit permeability increases which are induced by PGE_1, PGE_2 and other substances. A preliminary report was presented as a demonstration to the British Pharmacological Society (Crunkhorn & Willis, 1969).

Methods

Details of methods are given in a previous paper (Crunkhorn & Willis, 1971). Intradermal injections were made in the abdominal skin of female Wistar rats weighing 130–140 g, anaesthetized with methohexitone sodium (40 mg/kg, intraperitoneally). Increased local vascular permeability was visualized by the extravasation of pontamine blue 6BX. Mean diameter and intensity of the blue area were assessed from the underside of the skin. Intradermal injections were made

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in a volume of 0·1 ml in Tyrode solution; admixtures were made just before injection. Doses of histamine and 5-hydroxytryptamine (5-HT) refer to the base. The drugs used were prostaglandins E_1, E_2, $F_{1\alpha}$, $F_{2\alpha}$ (Upjohn), synthetic bradykinin (Sandoz), compound 48/80 (Burroughs Wellcome), methohexitone sodium (Lilly), pontamine blue 6BX (Edward Gurr), histamine acid phosphate and 5-hydroxytryptamine creatinine monosulphate.

Results

In initial experiments it was found that when $PGF_{2\alpha}$ was given intradermally as an admixture with PGE_2, the blueing reactions produced were far less severe than those to PGE_2 alone. When increasing doses of $PGF_{2\alpha}$ were given with PGE_2 (0·1 μg), it was found that 0·2–0·8 μg produced graded increases in inhibition; in all subsequent work a dose of 0·5 μg was used.

$PGF_{2\alpha}$ (0·5 μg) strongly inhibited responses to 0·1 μg doses of PGE_1 or PGE_2 (Fig. 1), but $PGF_{1\alpha}$ (0·5 or 1 μg) did not share this effect.

As shown in Fig. 2, $PGF_{2\alpha}$ (0·5 μg) failed to inhibit increases in permeability induced by histamine (1 μg) or bradykinin (1 μg) and the effect against 5-HT was

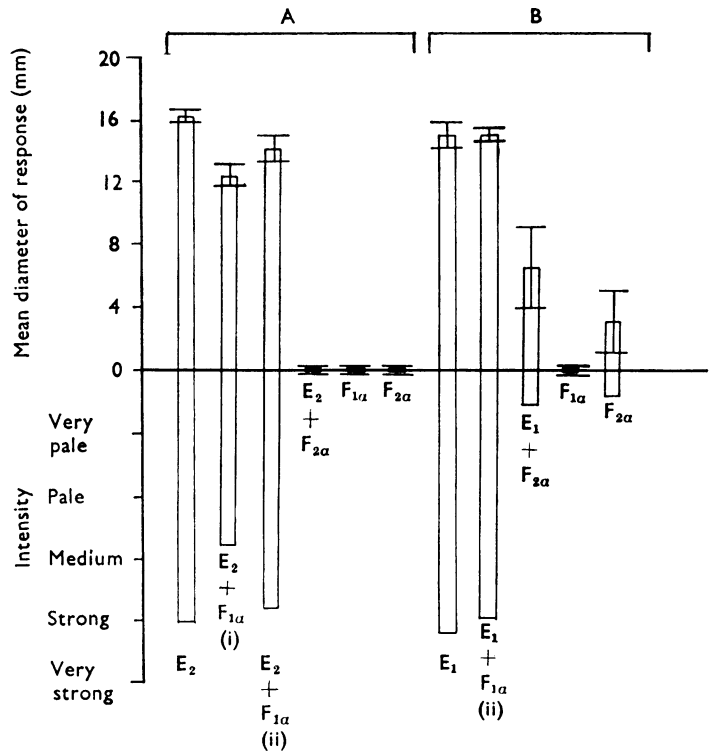

FIG. 1. Inhibition by $PGF_{2\alpha}$ but not by $PGF_{1\alpha}$ of skin blueing reactions induced by 0·1 μg of PGE_2 (in A) and PGE_1 (in B). In both experiments each of a group of five rats received six intradermal injections, namely: (E_2), 0·1 μg of PGE_2 given alone; ($E_2+F_{1\alpha}$), 0·1 μg of PGE_2 given in admixture with either 0·5 μg (i) or 1 μg (ii) of $PGF_{1\alpha}$; ($E_2+F_{2\alpha}$), 0·1 μg of PGE_2 in admixture with 0·5 μg of $PGF_{2\alpha}$; ($F_{1\alpha}$), 1 μg of $PGF_{1\alpha}$ given alone; ($F_{2\alpha}$), 0·5 μg of $PGF_{2\alpha}$ alone. In (B), 0·1 μg of PGE_1 (E_1) was used instead of PGE_2. Mean diameter (mm) ± S.E.M. and intensity of blueing are expressed separately.

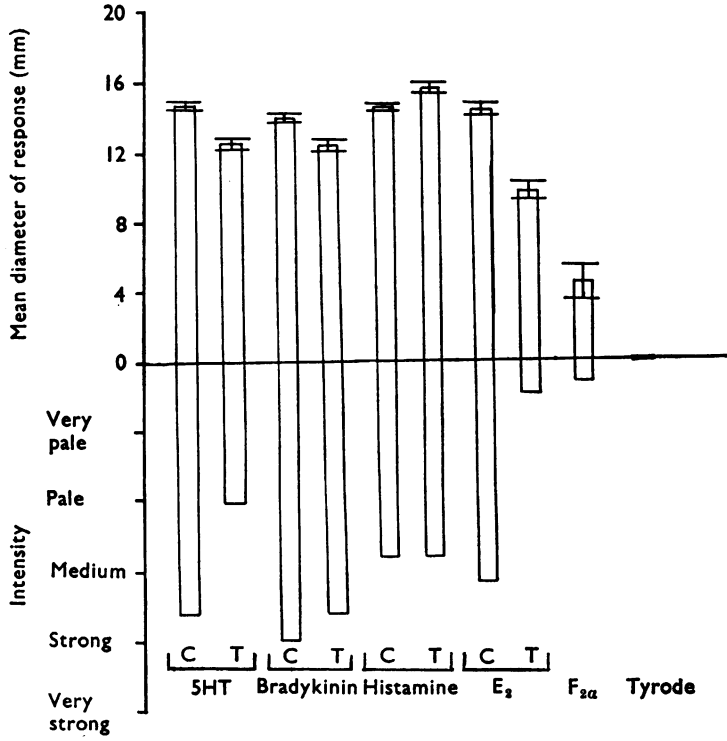

FIG. 2. Failure of $PGF_{2\alpha}$ to suppress blueing reactions induced by bradykinin, histamine or 5-hydroxytryptamine. A group of ten rats was used. The control sites (C) received intradermal injections of either 0·1 μg of 5-hydroxytryptamine (5-HT), 1 μg of bradykinin, 1 μg of histamine or 0·1 μg of PGE_2 (E_2). The test sites (T) received the same doses of bradykinin, histamine, 5-hydroxytryptamine or PGE_2, but given in admixture with 0·5 μg of $PGF_{2\alpha}$. In all the rats, one site was injected with 0·1 ml of Tyrode solution alone and six of the rats also received 0·5 μg of $PGF_{2\alpha}$ ($F_{2\alpha}$) given alone. Results are expressed as in Fig. 1.

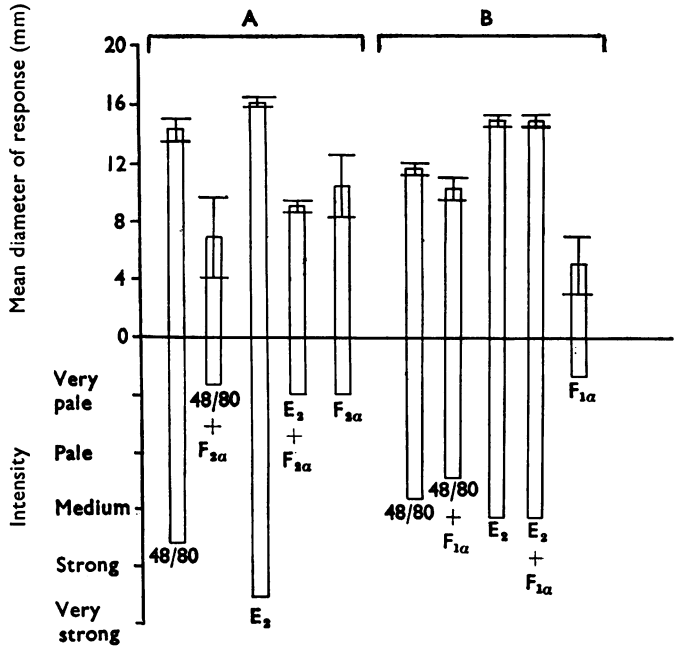

FIG. 3. Inhibition by $PGF_{2\alpha}$ of blueing reactions induced by compound 48/80. (A) Five rats each received 5 intradermal injections, namely: (48/80) 25 ng of compound 48/80 given alone; (48/80+$F_{2\alpha}$), 25 ng of 48/80 in admixture with 0·5 μg of $PGF_{2\alpha}$; (E_2), 0·1 μg of PGE_2 alone; (E_2+$F_{2\alpha}$), 0·1 μg of PGE_2 with 0·5 μg of $PGF_{2\alpha}$; ($F_{2\alpha}$), 0·5 μg of $PGF_{2\alpha}$ alone. (B) In a second group of five rats 0·5 μg of $PGF_{1\alpha}$ was used instead of $PGF_{2\alpha}$. Results are expressed as in Figs. 1 and 2.

slight. Reactions to the histamine releaser, compound 48/80 (25 ng), were inhibited by 0·5 μg of $PGF_{2\alpha}$ (Fig. 3), whereas $PGF_{1\alpha}$ (0·5 μg) had no inhibitory action.

Discussion

The relationship between the structure of the prostaglandins and their activity in various systems in different species follows no clear pattern (Bergström, Carlson & Weeks, 1968). In our study $PGF_{2\alpha}$ was unique among the prostaglandins tested. Whereas small doses of PGE_1 and PGE_2 induced increases in vascular permeability in rat skin, apparently by releasing histamine and 5-HT from the mast cells (Crunkhorn & Willis, 1971), the corresponding F-type analogues were virtually inactive. It seemed possible that F prostaglandins might have sufficient affinity for the same receptors as PGE to act as antagonists. Although $PGF_{2\alpha}$ inhibited per-

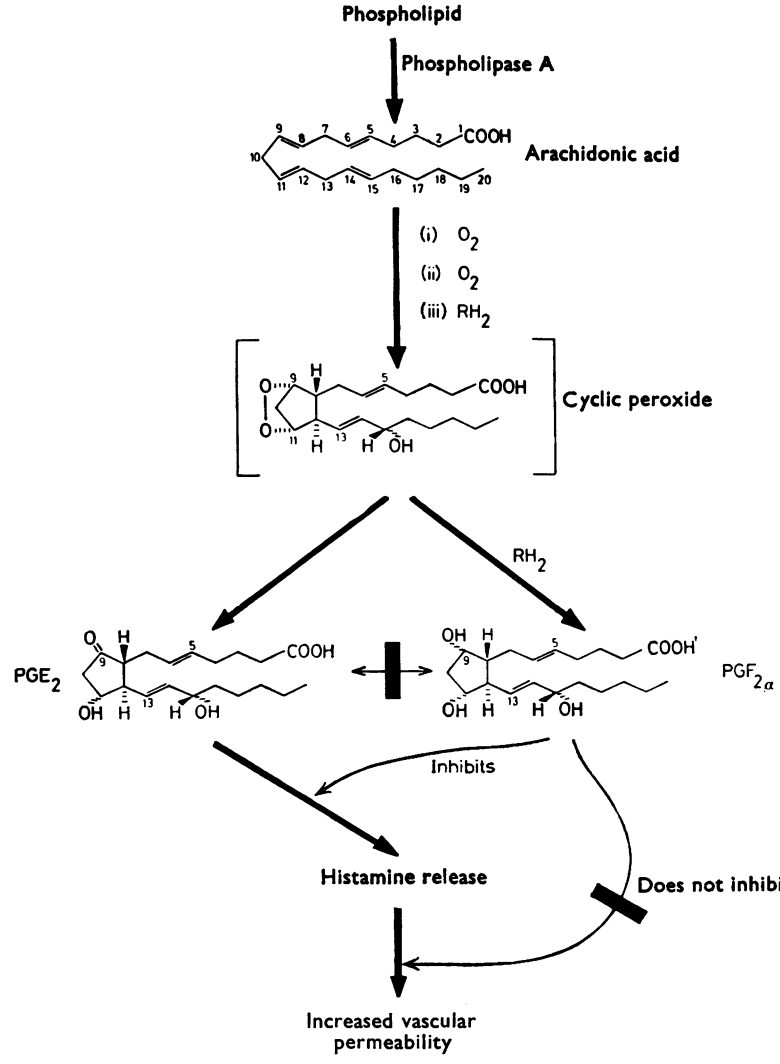

FIG. 4. A possible biochemical mechanism involved in local regulation of vascular permeability by the prostaglandins.

meability increases induced by PGE_1 and PGE_2, this effect was not shared by $PGF_{1\alpha}$. Our findings thus failed to support a general concept of interaction between the E and F groups of prostaglandins. Furthermore, this effect was not exclusive between pairs of E and F prostaglandins structurally identical except at position 9.

$PGF_{2\alpha}$ failed to suppress permeability increases induced by histamine and other agents acting directly on the microvasculature, and was therefore thought to interfere with the process of amine release from the mast cell. This hypothesis was supported by the observation that $PGF_{2\alpha}$ inhibited blueing reactions to compound 48/80, which is known to release histamine and 5-HT from rat mast cells (Moran, Uvnäs & Westerholm, 1962) whereas $PGF_{1\alpha}$ was inactive.

Histological examination has shown that increases in local vascular permeability in rat skin induced by compound 48/80 and by the E-type prostaglandins are accompanied by extensive mast cell degranulation (Crunkhorn & Willis, 1971), but we found that $PGF_{2\alpha}$ failed to cause a noticeable inhibition of this degranulation, even where it had largely or completely suppressed permeability increases to PGE_2 or 48/80. Degranulation was so marked in all areas receiving PGE_2 that mast cell counts were regarded as unnecessary. The results strongly suggest that $PGF_{2\alpha}$ exerts its protective action on the mast cell granule after this has been extruded.

Because of the similarity between the actions of compound 48/80 and the E-type prostaglandins, it might be inferred that they react with identical receptors on the mast cell. However, it is possible that 48/80 exerts its histamine releasing effect through local release of E-type prostaglandins. Enzyme inhibition studies have shown common features between the action of phospholipase A and compound 48/80 on isolated rat mast cells (Högberg & Uvnäs, 1957). In addition, phospholipase, which is present on the mast cell surface (Uvnäs, 1968) causes prostaglandin release (Vogt, 1967; Bartels, Vogt & Wille, 1968), probably by an initial release of arachidonic acid from cell membrane phospholipid (Vogt, Bartels, Kunze & Meyer, 1969).

The existence of a feedback mechanism between E-type prostaglandins and $PGF_{2\alpha}$ could be important in maintaining para-capillary circulation. $PGF_{2\alpha}$ might be released from nerve endings by antidromic stimulation in a way analogous to release of Irin (a mixture of prostaglandins) via stimulation of the trigeminal nerve (Ambache, Kavanagh & Whiting, 1965). Local control could also result from the preferential biosynthesis of E or F prostaglandins. The synthesis of PGE_1 and $PGF_{1\alpha}$ from their common precursor, dihomo-γ-linolenic acid has been extensively studied (Ryhage & Samuelsson, 1965; Nugteren & Van Dorp, 1965; Klenberg & Samuelsson, 1965; Nugteren, Beerthuis & Van Dorp, 1966; Samuelsson, 1965; Samuelsson, Granström & Hamberg, 1967; Hamberg & Samuelsson, 1967). Although the formation of PGE_2 and $PGF_{2\alpha}$ from arachidonic acid has received less attention it is probably very similar (Bergström, Carlson & Weeks, 1968). There is no interconversion between E and F prostaglandins. The formation of both types of prostaglandin follows a common biosynthetic pathway until the last stage (Fig. 4). Here the relative amounts of E and F prostaglandin formed from the cyclic peroxide are dependent upon the local oxidation-reduction conditions and the presence of co-factors (Van Dorp, 1967). Acute inflammation might thus involve a shift of synthesis from $PGF_{2\alpha}$ to PGE_2.

We are grateful to Dr. J. E. Pike of the Upjohn Company, Kalamazoo, for a gift of prostaglandins, to Burroughs Wellcome for compound 48/80, to Dr. W. E. Brocklehurst and

Dr. S. C. R. Meacock for advice and criticism, to Miss Patricia Baldock and Mr. P. L. d'Ambrumenil for technical assistance, and to Mr. P. Jenkins for histology and Mr. C. H. Cashin for photography.

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(*Received September* 24, 1970)