Acta derm.-venereol. 49: 251–261, 1969

CUTANEOUS VASCULAR REACTIONS TO PROSTAGLANDINS IN HEALTHY SUBJECTS AND IN PATIENTS WITH URTICARIA AND ATOPIC DERMATITIS

LENNART JUHLIN AND GERD MICHAËLSSON

Prostaglandins are a group of long-chain fatty acid compounds with alcoholic OH-groups which are essential for their biological activities. The name prostaglandin was coined by U.S. von Euler in 1934 since the active factor was extracted from the seminal fluid. Their chemistry and presence in different tissues have been clarified by Bergström and associates (3, 4). There are two groups of primary prostaglandins, labelled PGE and PGF, each containing three members. The PGE series (PGE_1, PGE_2, PGE_3) are dihydroxy compounds which can inhibit the contraction of human myometrium. The PGF series ($PGF_{1\alpha}$, $PGF_{2\alpha}$, $PGF_{3\alpha}$) are trihydroxy compounds which cause contraction of this muscle in man. There are also other differences in action between the E and F groups. The effects of prostaglandins have recently been reviewed (3, 6) and have also been described in two monographs (4, 7). The biological importance of these substances, especially with regard to extragenital tissues, is not completely known. In humans special interest has been devoted to the cardiovascular and metabolic effects of prostaglandins. The typical vascular action of the PGE compounds is dilatation of the small arteries with a resulting reduction in blood pressure.

In humans intravenous injection of PGE_1 in a dose of 0.1–0.7 μg/kg/min produces flushing of the face and a feeling of warmth and oppression lasting for 5–10 minutes after the end of injection (3). Intradermal injection of PGE_1 into human skin in doses of 1–5 μg results in prolonged erythema (18). The PGF compounds produce no or only a minor fall in blood pressure. In dogs and rats $PGF_{2\alpha}$ is reported to be a pressor substance.

In the investigation described below we compared the effects of intradermally injected PGE_1, PGE_2, $PGF_{1\alpha}$ and $PGF_{2\alpha}$. The reaction to PGE_1 was studied, further, in healthy subjects and in patients with urticaria, atopic dermatitis, eczematous dermatitis and psoriasis. The effects on the reaction to PGE_1 of various drugs which might give information about the mechanism of action of this prostaglandin were also investigated.

Material and Methods

Patients

Chronic urticaria: 15 patients, aged 22–49 years, had suffered almost daily attacks of urticaria for more than 6 months. They were not usually receiving treatment at the time of testing. Salicylates were found to be a contributory factor in four of the patients. Otherwise the cause of the urticaria remained obscure. Immediate or delayed demographism was not seen in any of these patients.

Acute urticaria: 5 patients, aged 22–49 years were tested during the acute urticarial eruption and before any treatment had been given.

Factitious urticaria: 5 patients, aged 22–37 years.

Cold urticaria: 2 patients, aged 21 and 55 years showed a typical urticarial reaction on exposure to ice cubes.

Department of Dermatology, University Hospital, Uppsala, Sweden.

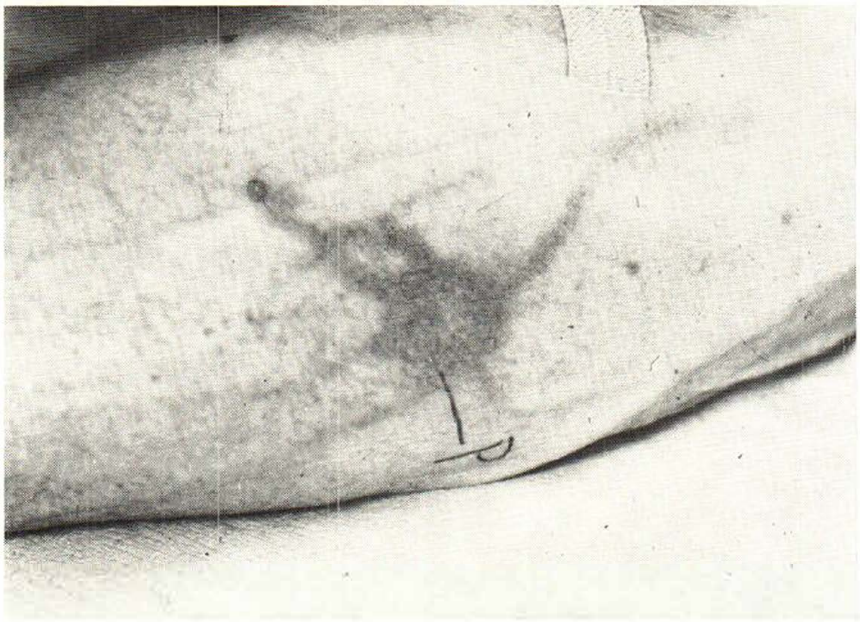

Fig. 1. Erythematous reactions with streak over lymph vessels 60 minutes after intradermal injection of 5 μg of PGE_1.

Cholinergic urticaria: 3 patients, aged 19, 22 and 25 years showed small typical wheals on exposure to heat.

Hereditary angioneurotic edema: 2 patients, aged 25 and 49 years, are described in detail elsewhere.

Atopic dermatitis: 15 adult patients (13 of them aged 18–25 years and two 34 and 55 years) with widespread atopic dermatitis of varying severity but in all cases requiring hospital care in the wards. The skin areas used for tests were often somewhat lichenified and dry.

Nonspecific eczematous dermatitis: 17 patients, aged 20–66 years. The test sites were free from dermatitic changes.

Various: This group comprised 47 patients with psoriasis, leg ulcer, pemphigus, discoid erythematodes, dermatitis herpetiformis, porphyria cutanea tarda, acne vulgaris, Dercum's disease and various minor skin disorders.

Controls: Nineteen apparently healthy men and women, mostly hospital staff, aged 22–42 years, served as controls.

Intradermal injection of prostaglandins

Intradermal injections of 0.001–5 μg of prostaglandins in 0.1 ml saline were given on the volar side of the forearm unless otherwise stated. They were prepared from a stock solution containing 50 μg/ml.[1] The area of the erythema was estimated by measuring the diameters and assuming that they were regular ellipses. The occurrence of red streaks from the test area was also noted but not included in the measured area. All measurements were made by the authors at 20 minutes and at 1, 2, 5 and 24 hours after the injection.

Intravenous retrograde injection of drugs

A vein on the forearm was cannulated with a plastic catheter. The hand and forearm were exsanguinated by an Esmarck rubber bandage and a blood pressure tourniquet was applied on the upper arm and set at 250 mm Hg. The cannulated vein was emptied of residual blood, and saline was then injected on the side used as a control.

[1] Kindly supplied by Professor Sune Bergström, Department of Medical Chemistry, Karolinska Institutet, Stockholm, Sweden.

It was considered desirable that the volume injected should amount to about 60–80 ml to obtain enough pressure within the vein to force the fluid injected into the capillary bed. PGE_1 was injected intradermally 3–5 minutes later. The duration of arterial occlusion was 20 minutes. The other arm was then treated in the same way except that the active substance was now added to the saline injected. In those cases where the drug could not be injected in an appropriate volume because of pain, saline was given in addition. Before releasing the tourniquet an attempt was made to withdraw the injected solution in order to reduce release of the active substance into the general circulation.

Estimation of sweat response. The sweat response to drugs was measured by applying one drop of 5 per cent o-phthaldialdehyde in xylene 10–15 minutes after the intradermal injection of the test solutions. The functioning sweat pores were then stained black (13). Their number per cm^2 was counted and compared with a saline injected control area.

Results

Cutaneous reactions to prostaglandins E_1 and E_2 in healthy subjects

Intradermal injection of 1–5 μg of PGE_1 and PGE_2 produced an intensive dark red erythema. Twenty minutes after the injection a swelling of about 5 × 5 mm usually remained centrally in the erythematous patch, but there was no tendency to wheal-ing. The margin of the area was somewhat diffuse initially but one hour after injection it was quite distinct. The intensity of the erythema was now maximally pronounced with a hyperalgesic homogeneous deep red area. In 9 of 12 healthy subjects irregular red streaks were now seen extending from the margins of the red area, mostly in a proximal direction (Fig. 1). They were usually a few centimeters long but in two subjects a streak continued to the axilla, apparently localized over the lymphatic vessels leading from the injected area. The streaks were maximal at one hour and had usually disappeared after two hours. The erythematous reaction to 1–5 μg PGE_1 and PGE_2 persisted for 4–10 hours. The size of these reactions at different times after injection are given in Table I. One hour after injection the red area was painful to slight touch. This hyperalgesia persisted as long as there was any visible erythema. It was not experienced along the red streaks.

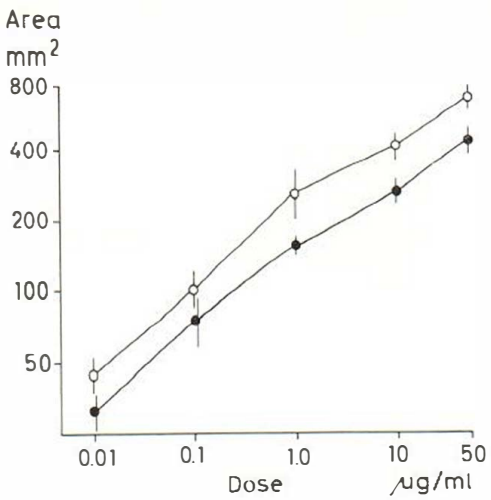

Fig. 2. Erythema produced by different doses of PGE_1 ○—○ Area 20 minutes after i.c. injection of PGE_1 ●—● Area 60 minutes after i.c. injection of PGE_1.

The dose-response curve for 0.001–5 μg PGE_1 injected in 0.1 ml saline in the forearm is shown in Fig. 2. Thus 1 ng (nanogram) of PGE_1 was sufficient to produce an erythema persisting for about one hour, which was not seen in the saline injected control area. No hyperalgesia nor erythematous streaks occurred with 1 ng of PGE_1 but these were produced by 10 ng in 5 and 3, respectively, out of 9 subjects tested.

Comparison of effects of prostaglandins E_1, E_2 F_{1a} and F_{2a}

The dose response to the prostaglandins was compared simultaneously in the skin of the back in 22 subjects as follows: controls 4, atopic dermatitis 5 and various types of urticaria 13 (chronic 7; factitious 1; cold 2; heat 3). The positions of the injections

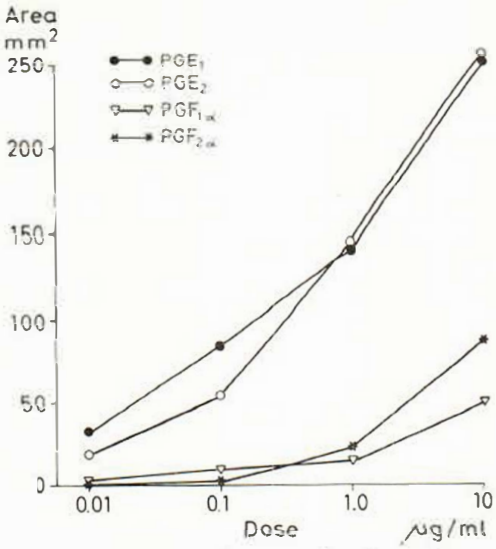

Fig. 3. Areas of erythema produced one hour after i.c. injection of prostaglandins in the skin of the back of 22 patients. Injected volume 0.1 ml.

were alternated to eliminate regional differences in response. No difference in effect was found betwen PGE_1 and PGE_2 (Fig. 3). Prostaglandins $F_{1\alpha}$ and $F_{2\alpha}$ produced a non-tender erythema lasting for 1–2 hours which was weaker and of smaller dimensions than that of PGE_1 and PGE_2 and did not show the extending streaks of the PGE group. Thus a 1000 times greater dose of $PGF_{1\alpha}$ was needed to produce about the same area of erythema as 0.01 µg of PGE_1. The mean area of erythema produced by 1 µg of $PGF_{2\alpha}$ was twice that of $PGF_{1\alpha}$. The means of the ratios of the erythematous areas produced by 1 µg of $PGF_{1\alpha}$ and PGE_1 were 0.24 and 0.17 at 20 minutes and one hour, respectively. The corresponding ratios for $PGF_{2\alpha}$ and PGE_1 were 0.43 and 0.33. The relationship in response between the four prostaglandins tested was approximately the same for patients with atopic dermatitis, patients with urticaria and control subjects.

Tachyphylaxis

Injections of 5 µg of PGE_1 in 0.1 ml saline were given in 7 healthy subjects into the same site of the forearm at 0 and 24 hours. In three of them injections were also given at 48 hours. The erythema showed a 25–30 % decrease in size 20 minutes after the second and third injections, whereas it was the same after 1–5 hours. The erythematous streaks were slightly less pronounced on repeated injections. The hyperalgesia was unchanged or increased. Daily intradermal injections of 0.1 and 1 µg of PGE_1 into the same sites during 3 days in four subjects produced exactly the same area of erythema each day.

Sweating

None of the intradermally injected prostaglandins produced any increase in sweating.

Reactions to prostaglandins in patients with urticaria

Compared with other subjects, the 15 patients with chronic urticaria showed a tendency to whealing 20 minutes after the injection of PGE_1. This was not present to the same extent in the saline injected control areas. The erythema produced by PGE_1 lasted longer and was significantly greater in size than in healthy subjects at 2–5 hours (Table 1). In one of the patients who was sensitive to salicylates, the intradermal injection of 5 µg PGE_1 produced a generalized urticarial eruption. This started in the erythematous streaks leaving the test site on the forearm, and progressed along the upper arm and chest of the same side and then to both inguinal regions. The same pattern of reaction was found after two repeated tests. In four other patients with chronic urticaria minute wheals were seen around the PGE_1 test site on the arm. Two of these patients were also tested with other prostaglandins in the skin of the back. One hour after the injections urticarial wheals appeared around the sites where the prostaglandins E_1, E_2, $F_{1\alpha}$ and $F_{2\alpha}$ had been injected. They were most pronounced around areas where the highest doses of PGE_1 and PGE_2 had been given.

In patients with acute, cold, heat and factitious urticaria, as well as in two patients with hereditary angioneurotic edema the reactions to PGE_1 and PGE_2 were the same as in normal subjects.

Table 1. *Size of the erythematous reaction at various times after intradermal injection of 5 μg PGE_1*

Diagnosis	No. of patients	Mean area of erythema in mm² ± SE of the mean at various times after injection				
		20	1h	2h	5h	24h
Controls	12	681 ± 116	421 ± 59	186 ± 26	68 ± 29	8 ± 7
Chronic urticaria	15	548 ± 109	529 ± 100	368 ± 55**	319 ± 82**	90 ± 53
Acute urticaria	5	341 ± 52	411 ± 68	289 ± 67	71 ± 39	0
Factitial urticaria	5	754 ± 133	568 ± 177	246 ± 71	118 ± 50	0
Cold urticaria	2	347 — 1256	353 — 416	314 — 294	236 — 0	236 — 0
Hered. angion. edema	2	432 — 895	687 — 314	612 — 188	550 — 94	471 — 94
Atopic dermatitis	10	251 ± 46**	254 ± 54	228 ± 63	109 ± 44	0
Non spec. dermatitis	12	509 ± 114	437 ± 60	257 ± 47	59 ± 27	12 ± 9
Psoriasis	9	723 ± 211	344 ± 40	252 ± 34	109 ± 33	0
Various	12	558 ± 145	472 ± 53	215 ± 48	71 ± 38	0

** Probability that the values differ from controls <0.01

Reactions to prostaglandins in patients with atopic dermatitis and various dermatoses

In patients with atopic dermatitis the erythematous area produced by PGE_1 was significantly smaller at 20 minutes than in the controls (Table 1). Subsequently no significant differences were observed with regard to erythematous streaks and pain. In one patient with severe atopic dermatitis the intense erythema produced by 5 μg of PGE_1 was surrounded by a pale 2 cm broad zone. Lower doses of PGE_1 caused erythema without peripheral blanching, as also did a repeated test with 5 μg after oral administration of a total of 100 mg of prednisone during the previous 24 hours. When prostaglandins E_1, E_2, $F_{1\alpha}$ and $F_{2\alpha}$ were injected in the skin of the back in 5 patients with atopic dermatitis the area of erythema did not differ significantly from those seen in normal subjects and in patients with urticaria. Patients with psoriasis and various other skin disorders showed reactions to PGE_1 which did not differ from those of the control group (Table 1).

Influence of vasoactive drugs on the reaction to PGE_1: Blockade of adrenergic α-receptors

Phenoxybenzamine hydrochloride[2] (0.1 mg/1 ml saline) was given by retrograde intravenous injection in an occluded arm to 5 patients (chronic urticaria 3, Dercum's disease 1, palmar hyperhidrosis 1). The doses were 0.8–0.6 mg per 1000 ml of arm volume occluded, *i.e.*, totally 1.2–3.8 mg. The same volume of saline alone was injected in the control arm, which was treated first. When compared with the saline treated side the phenoxybenzamine injected arm showed an increased skin temperature and a decreased vasoconstrictor and pilomotor response to epinephrine given by a quantitative iontophoretic method (9). The sweat response to epinephrine was also decreased on the phenoxybenzamine treated arm. The difference between the reactions in the arms was noted for at least 12 hours. The effect of α-receptor blockade on the reaction to intradermally injected PGE_1 5 μg varied somewhat. Thus one hour after injection of PGE_1 the erythematous area was decreased in two of the patients with urticaria and increased in the other patients. The erythema seen after 20 minutes and 2 hours was about the same on the treated and on the control arm.

Blockade of adrenergic β-receptors

In two subjects 2.4 mg isopropylaminopropanol[3] was given by retrograde intravenous injection into an occluded arm. The reac-

[2] Dibenzyline,® Smith, Kline & French Lab. Ltd., Philadelphia.
[3] Aptin,® AB Hässle, Gothenburg, Sweden.

Table 2. *Inhibition of the erythematous reaction of PGE_1 by intravenous infusion of 800.000 IU of Trasylol*

Dose of PGE_1 intradermally	Diagnosis	No. of Patients	Quotient ± SE of erythematous area after/before treatment with Trasylol	
			20 min.	60 min.
5 μg	Chronic urticaria	5	0.65 ± 0.21	0.62 ± 0.13
5 μg	Various disorders	5	0.59 ± 0.08	0.86 ± 0.13
5 μg	Chron. urt. + var.dis.	10	0.62 ± 0.10**	0.74 ± 0.08**
1 μg	Chron. urt. + var.dis.	5	0.89 ± 0.08	0.82 ± 0.15
0.1 μg	Chron. urt. + var.dis.	5	0.88 ± 0.10	0.78 ± 0.16

** $P < 0.01$ P = The probability that the differences between the quotients and 1.00 is caused by random factors.

tion to 5 μg of PGE_1 was decreased by 25–40 per cent at 20 minutes, but after one hour it was the same as in the saline treated control side. In eight subjects with various skin disorders, cutaneous infiltration of 0.8 mg of the β-blocking agent in 0.8 ml saline was given 30 minutes before injection of PGE_1. The PGE_1 induced erythema seen at one hour was decreased at the site of injection of the β-blocking agent compared with the saline pretreated control site. Twenty minutes, one hour and two hours after PGE_1 injection the ratios of erythema on isopropylaminopropanol treated and saline treated skin were 0.83 ± 0.14, 0.61 ± 0.07 and 0.81 ± 0.12, respectively. In three patients with atopic dermatitis no difference was seen when PGE_1 was injected in such treated skin. Injection of isopropylaminopropanol produced a slight anesthesia which lasted for about 30–60 minutes.

Antihistamines and antibradykinins

Promethazine (15–20 mg in 80 ml saline) was injected intravenously into the occluded arm in each of two patients with chronic and cold urticaria, respectively. Thiaxanthene[4] (1 mg in 80 ml), which is also an antibradykinin, was injected in the same way into a patient with factitious urticaria. The reactions to histamine (0.1 ml, 1/10.000) in the blocked arms were smaller than in the control arms in all patients. The sensitivity to ice in the patient with cold urticaria and the dermographism in the patient with factitious urticaria were also less marked in the blocked than in the control arm. The reactions to 5 μg PGE_1 were, however, the same in both arms. Intramuscular injection of 5 mg thiaxanthene in two patients with chronic urticaria decreased the histamine flare and the bradykinin erythema but did not change the reactivity to 5 μg of PGE_1 injected one hour later.

Atropine

One patient with palmar hyperhidrosis and psoriasis was treated with an intravenous retrograde injection of 0.24 mg atropine in 60 ml saline. No sweating of the treated palm was seen for at least 6 hours. The sweating produced by metacholine (0.1 ml–1/1000) was also inhibited on the palm of the atropine treated side but not on the control side. The erythematous reaction produced by 5 μg of PGE_1 was the same on both arms.

In eight subjects a deep intradermal injection of 0.1 mg of atropine in 0.5 ml saline was given into two sites and saline alone into two other sites. In the atropine treated area the reddening produced by intradermal injection of metacholine (1/1000) one hour later was decreased. The erythema produced by 0.1 and 1 μg of PGE_1 was, however, the same in the atropine and saline treated skin.

[4] BP 400, Sandoz, Basel.

Table 3. *Vascular reactions to mixtures of epinephrine and PGE_1 injected intradermally in 7 patients*

Dose µg/ml		Reactions at 20 and 60 minutes after injection	
PGE_1	Epinephrine	20	60
50	100	Erythema	Erythema
10	10	Erythema	Erythema
1	1	Erythema	Erythema
10	100	Central erythema + blanching zone + flare* (10–15 mm diam) (4–8 mm) (15–20 mm)	Erythema
1	10	Central erythema + blanching zone + flare* (10–15 mm diam) (4–8 mm) (15–20 mm)	Erythema
1	100	Central erythema + blanching zone + flare* (10–15 mm diam) (4–8 mm) (15–20 mm)	Central erythema + blanching zone
0.1	10	Central erythema + blanching zone + flare* (10–15 mm diam) (4–8 mm) (15–20 mm)	Central erythema + blanching zone
0.1	100	Blanching and flare*	Blanching
0	10	Blanching and flare*	Blanching

* The flare was seen in three of the subjects tested.

Kallikrein inhibitor

Intravenous infusion of Trasylol[5] (800 000 KIU) decreased the erythema produced by PGE_1 in 5 patients with chronic urticaria of unknown etiology. The erythema induced by 5 µg PGE_1 also decreased after Trasylol in 5 patients with pemphigus vulgaris, psoriasis, acute urticaria, stomatitis, dermatitis herpetiformis (Table 2). Lower doses (0.1–1 µg) of PGE_1 were also given in 5 patients. The effect of Trasylol was less marked in these cases (Table 2). When the whole material was taken together the ratios of the erythematous areas produced by 5 µg of PGE_1 after and before Trasylol were 0.62 ± 0.10 and 0.74 ± 0.08 at 20 and 60 minutes. The ratios are significantly less than 1.0; $p < 0.01$.

Epinephrine

Mixtures of epinephrine and PGE_1 were injected intradermally in 6 control patients and one patient with atopic dermatitis. They all showed the same pattern of reaction (Table 3). The addition of 1–10 µg/ml of epinephrine to 10 µg/ml of PGE_1 did not change the erythema produced after intracutaneous injection of PGE_1 alone. When 100 µg/ml of epinephrine was injected with 10 µg/ml of PGE_1 a central erythema surrounded by a pale zone was seen at 20 minutes. The pale ring was surrounded by a diffuse erythematous flare in 3 subjects. A similar type of reaction was seen after administration of a mixture of 1 µg PGE_1/ml + 10 µg of epinephrine/ml. When the proportion of epinephrine was increased the same pattern was obtained but the peripheral blanching was still observed one hour after the injection (Table 3). A mixture of 0.1 µg of PGE_1 + 100 µg of epinephrine produced blanching which was surrounded by a flare in 3 subjects. A flare was also seen, however, around the blanching caused by injection of epinephrine alone.

Histamine depletion

In four patients the skin was pretreated by iontophoresis of histamine in water (10 mg/ml; 3 mA for 4 minutes). The procedure was repeated daily for three days. The reaction to histamine decreased during these treatments. One hour after the third iontophoresis no reaction to histamine was seen. Injection of 0.1 mg of PGE_1 now produced the same reaction in the treated area as in a non-treated area. In 9 other

[5] Trasylol,® Bayer AG, Leverkusen, Germany.

patients the skin was pretreated similarly for 3 days by iontophoresis of compound 48/80 (0.1 mg/ml; 3 mA, 4 minutes). Two hours after the last iontophoresis PGE_1 was injected intradermally. The area of erythema produced by PGE_1 1 μg (9 subjects) and 0.1 μg (5 subjects) was the same on the 48/80 treated side and on the control arm (pretreated with iontophoresis of distilled water 5 subjects and nontreated 4 subjects).

Because of a fairly moderate initial response to iontophoresis of compound 48/80 seven patients were given daily intradermal injection of 0.1 ml of compound 48/80 (1 mg/ml) for 3 days. On the third day only minimal whealing occurred. Saline was used for the control area. The response to 0.1 μg of PGE_1 was, however, the same in the compound 48/80 and control areas. Daily application of tetrahydrofurfurylnicotinate ointment[a] for 3 days in 6 control subjects and 7 patients with various minor skin disorders did not influence the reaction to 5 μg of PGE_1.

Corticosteroid treatment

Treatment for 12 hours with 0.2 % fluocinolone cream under an occlusive dressing in 10 subjects resulted in blanching of the treated area as compared with control areas treated with the base of this cream alone. Intradermal injection of 0.1–1 μg of PGE_1 produced a smaller erythema on the fluocinolone area than on the control area. At 20 minutes after injection the PGE reaction on the fluocinolone side showed distinct borders in contrast to diffuse borders on the control area. No red streaks were seen on the fluocinolone treated skin but were always present on the control area. The mean ratios ± SE of the erythematous areas produced by 1 μg PGE_1 on the fluocinolone and control treated skin were 0.62 ± 0.09 and 0.52 ± 0.13 at 20 and 60 minutes, respectively. The corresponding values for 0.1 μg PGE_1 were 0.68 ± 0.09 and 0.74 ± 0.08.

[a] Trafuril,® CIBA, Basel.

Local anesthesia

In 6 subjects the skin of one arm was injected with 1 % lidocaine and the skin of the other with saline 20 minutes before a test injection with 1 μg of PGE_1. The flare surrounding the erythema 20 minutes after the injection of PGE_1 was absent on the anesthetized area. Distinct margins were seen on this side in contrast to the diffuse borders of the initial PGE erythema on the control side. There was no difference in area or intensity of the erythematous reaction at 1–5 hours. The same type of reaction was seen in two subjects given the longer acting 1 % mepivacaine before test injection with 1 μg of PGE.

Discussion

That PGE_1 is a powerful vasodilator in animal and human skin has recently been shown by Solomon *et al.* (18). In this investigation we have studied its effects further in healthy subjects and in patients with various forms of dermatosis. From the dose-response curve (Fig. 2) it is evident that intradermal injection of as little as 1 ng is enough to produce erythema in a normal skin. With higher doses the erythema was more intense and persisted for several hours. PGE_2 was found to be as effective a vasodilator as PGE_1 whereas $PGF_{1\alpha}$ and $PGF_{2\alpha}$ were less potent in this respect. The PGE compounds also produced a characteristic hyperalgesia which did not occur after $PGF_{1\alpha}$, $PGF_{2\alpha}$, kallikrein, bradykinin or histamine (12).

The erythematous streaks leading away from the site of injection of PGE_1 and PGE_2 were not seen after PGF injections. They seemed to follow the lymph vessels and were probably caused by a leakage of the prostaglandins from the lymphatics to the surrounding blood vessels. This reaction had much in common with the appearance of a lymphangitis, but there was no lymphadenitis. The reason for the absence of streaks after injection of other vasodilator drugs might be that these are more

easily carried away or destroyed than the PGE compounds.

The erythema seen 2–5 hours after intradermal injection of prostaglandins was more pronounced in patients with chronic urticaria than in other subjects. Five patients also reacted with minute urticae around the injected area after one hour. In one of them the injection gave rise to a generalized urticaria. No positive dermographism was found in these patients and similar reactions were not seen after intradermal injection of histamin. Bradykinin and kallikrein produced increased erythematous reactions at 2–5 hours but no urticaria. We have at present no definite explanation for the elicitation of urticarial wheals by prostaglandins in these patients.

Patients with atopic dermatitis reacted with blanching 30–90 minutes after administration of other common vasodilators such as metacholine, bradykinin, tetrahydrofurfurylnicotinate and histamine but showed an erythematous reaction to PGE_1. The size of the erythema did not differ significantly from that in healthy subjects, with the exception that it was smaller at 20 minutes, which was probably due to lack of a flare. In one patient a zone of peripheral blanching was seen outside the red area caused by 5 μg of PGE_1 but not outside reddening produced by lower doses of this prostaglandin. A possible explanation for the blanching might be that the higher dose of PGE_1 released histamine or kinins, since they were found to produce blanching in this patient.

The mechanism for the erythema and hyperalgesia produced by the PGE compounds is not known. The reaction has much in common with that described by Bayliss as antidromic vasodilatation (5, 17 for ref.). The term antidromic was used because the vasodilator impulses run centrifugally in the sensory fibers. Lewis assumed that these fibers were also responsible for the spread of hyperalgesia but not for pain (14). Typical of antidromic vasodilatation is a delayed and prolonged response to a brief stimulus. Histamine or acetylcholine has earlier been assumed to mediate this response. Unknown substances which are not antagonized by antihistamines and atropine have been found more likely, however, to be the mediators (5, 17). We found that the vascular effect of PGE_1 was not changed by antihistamines, histamine depletion or atropine. Prostaglandins have been found in the spinal cord and they are released on nerve stimulation (3, 7). They therefore seem to fill the criteria as possible mediators for antidromic vasodilatation.

The PGE, induced erythema in skin pretreated with fluocinolone cream under an occlusive dressing had more distinct borders and a smaller area than in the control treated skin. It might therefore be possible that the initial erythema produced by PGE_1 is composed of a central reddening caused by a direct effect on the vessels and a surrounding flare mediated by an axon reflex. The decrease in erythema at 20 minutes could then be caused by an inhibition of a PGE_1 induced flare. In fluocinolone treated skin we observed previously such an inhibition of the flare reaction produced by metacholine, histamine and serotonin (10). An inhibition of the erythema is also seen after 20 minutes, but not after one hour, in skin pretreated with lidocaine, thus supporting the hypothesis that part of the erythema might be due to an axon reflex. The fluocinolone produced inhibition was, however, also seen after one hour when usually the flare would have disappeared. This and the decrease by fluocinolone of theerythematous streaks might be caused by an inhibition of the spreading of PGE_1 or a decrease in reactivity to the direct vasodilator effects of PGE_1.

The adrenergic nervous system has two types of peripheral receptors called α and β (2). A stimulation of the α-receptors gives vasoconstriction and that of β-receptors vasodilatation. Janowitz assumed in 1949 that in human skin there were only α-receptors (8). During recent years more specific β-blocking drugs such as isopropylaminopropanol and propanolol have become available (1), making it possible to

[7] Synalar® 0.2 % cream, Scanmeda, Gothenburg, Sweden.

better differentiate the receptors. Thus Öberg and Rosell showed that vasodilatation in subcutaneous tissues can be inhibited by a blockade of β-receptors (16). Preliminary results also suggest that there are β-receptors intradermally (15). A blockade of the α-adrenergic receptors was achieved here by retrograde intravenous injection of dibenzyline. If the vasodilator effect of PGE_1 is to some extent inhibited by stimulation of the α-receptors, blocking of these receptors might give an increased vasodilatation. We could not find any definite effect of such α-receptor blockade on the erythema produced by 5 μg of PGE_1.

Injection of a β-blocking agent was made with the same technique. Here PGE_1 produced a smaller erythema on the blocked arm at 20 minutes. This might be due to the anesthetic properties of the β-blocking agent, since at 20 minutes intradermal injection of lidocaine also can inhibit the PGE_1 induced erythema. In skin pretreated with dermal infiltration of the β-blocking agent, however, the erythema caused by PGE_1 was reduced also at 60 minutes. At this time it is less probable that the decrease in erythema was due to an inhibition of the flare caused by the local anesthetic properties of the drug. It is more likely to be explained by a blockade of the adrenergic β-receptors since the anesthesia produced by isopropylaminopropanol is weak in the doses used and a similar pretreatment with 1 % lidocaine gave a better and longer lasting anesthesia but no difference in the reaction to PGE_1 at 60 minutes. The effects of adrenergic receptor blocking agents on the actions of prostaglandins in other tissues seem to depend upon the organ and species tested.

The prostaglandins usually inhibit the actions of epinephrine. We found that 100 μg/ml of epinephrine is needed to overcome the vasodilatation produced by simultaneous intradermal injection of 0.1 μg/ml of PGE_1. The central erythema with surrounding blanching seen when 1–10 μg/ml of PGE_1 was used might be explained by a concentration of the prostaglandins around the site of injection whereas epinephrine has a tendency to a spreading towards the periphery. Thus when epinephrine alone was injected intradermally the blanched area often moved outwards, with a simultaneous central disappearence.

In patients with chronic urticaria the edematous reaction to kallikrein was inhibited by intravenous injection of a kallikrein inhibitor, Trasylol (11). The reactions to 5 μg of PGE_1 at 20 and 60 minutes were decreased by Trasylol in 5 patients with chronic urticaria and 5 with various disorders. No inhibition of reactions to lower doses of PGE_1 was observed. It is possible, therefore, that the high doses of prostaglandins might activate kallikrein and/or cause an increased erythema by liberation of kinins, which is prevented by Trasylol. Further studies are needed, however, to elucidate the mechanism involved.

SUMMARY

The effects of intradermally injected prostaglandins E_1 (PGE_1) were studied in healthy subjects and in patients with various types of urticaria, atopic dermatitis, psoriasis and eczematous dermatitis. In all subjects intradermal injection of 1 ng–5 μg of PGE_1 gave a characteristic erythematous reaction lasting for 1–10 hours. Hyperalgesia and erythematous streaks from the test site along the lymph vessels were induced with doses above 10 ng. The effects of PGE_1 were also compared with those of intradermally injected prostaglandin E_2 (PGE_2), prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). PGE_2 had essentially the same effect on the skin as PGE_1. The erythema seen after PGF_1 and PGF_2 was considerably smaller than that produced by PGE_{1-2} and neither erythematous streaks nor hyperalgesia were present. In patients with chronic urticaria the erythematous reaction to PGE_1 was greater and more prolonged than in controls. Five of 15 patients developed wheals around the test site and one patient showed a generalized urticaria starting along the erythematous streaks. The explanation for this is not known. In patients with atopic dermatitis 5 μg of PGE_1 i.c. caused an erythematous reaction which contrasted with the blanch-

ing seen after other vasodilators such as histamine and bradykinin. The size of the erythema was initially decreased, probably due to the absence of a flare. Regional blockage of the α-adrenergic receptors with dibenzyline was without certain effect on the PGE_1 induced erythema. After intradermal infiltration of the skin with a β-adrenergic blocking agent the PGE_1 reactions were reduced. Similar pretreatment with lidocaine 1 % influenced the PGE_1 reaction at 20 minutes but not later. In skin pretreated with 0.2 % fluocinolone actonide cream under an occlusive dressing the response to PGE_1 was reduced by 50 %. This might have been due either to an inhibition of the spreading or to decrease in reactivity to the direct vasodilator effects of PGE_1. Large doses of epinephrine are required to inhibit the vasodilatory effects of PGE_1. Thus 100 μg of epinephrine is needed to abolish the effects of 0.1 μg of PGE_1. The reaction to PGE_1 was not influenced by histamine depletion, antihistamines or atropine. Intravenous infusion of a kallikrein inhibitor reduced the effects of high but not of low doses of PGE_1. It is suggested that PGE_1 might be one of the main mediators of antidromic vasodilatation and an important factor in inflammatory response.

Acknowledgement

For generous supply of the prostaglandins we wish to thank Professor Sune Bergström, Department of Medical Chemistry, Karolinska Institutet, Stockholm.

This investigation was supported by grants from the J. Schaumann foundation and the Swedish Medical Research Council (Project No. B68-19X-769-04A).

REFERENCES

1. Ablad, B., Brogård, M. and Ek, L.: Pharmacological Properties of H 56/28—a β-Adrenergic Receptor Antagonist. *Acta pharmacol.* 25: 9, Suppl. 2, 1967.
2. Ahlqvist, R. P.: Development of the Concept of alpha and beta Adrenotropic Receptors. *Ann. N. Y. Ac. Sci.: 139:* 549, 1967.
3. Bergström, S., Carlsson, L. and Weeks, J. R.: The Prostaglandins: A family of biologically active lipids. *Pharmacol. Rev. 20:* 1, 1968.
4. Bergström, S. and Samuelsson, B.: *Prostaglandins.* Nobel Symposium 2. Almqvist & Wiksell, Stockholm, 1967.
5. Chapman, L. F. and Goodell, H.: The Participation of the Nervous System in the Inflammation Reaction. *Ann. N. Y. Ac. Sci. 116:* 990, 1964.
6. Euler, U. S. v.: Prostaglandins. *Clin. Pharmacol. Ther. 9:* 228, 1968.
7. Euler, U. S. v. and Eliasson, R.: *Prostaglandins.* Medicinal Chemistry Monographs Vol. 8. Academic Press N. Y., 1967.
8. Janowitz, H., Sonnenschein, R. R. and Grossman, M. J.: Adrenotropic Receptors of the Human Skin. *J. Invest. Derm. 12:* 205, 1949.
9. Juhlin, L.: Skin Reactions to Iontophoretically Administered Epinephrine and Norepinephrine in Atopic Dermatitis. *J. Invest. Derm. 37:* 201, 1961.
10. Juhlin, L.: Vascular Reactions in Skin Treated with Fluocinolone. *Acta derm.-venereol.* (Stockholm) *44:* 322, 1964.
11. Juhlin, L. and Michaëlsson, G.: Use of a Kallikrein Inhibitor in the Treatment of Urticaria and Hereditary Angioneurotic Edema. *Acta derm.-venereol.* (Stockholm) *49:* 37, 1969.
12. Juhlin, L. and Michaëlsson, G.: Cutaneous Reactions to Kallikrein, Bradykinin and Histamine in Healthy Subjects and in Patients with Urticaria. *Acta-derm.-venereol.* (Stockholm) *49:* 26, 1969.
13. Juhlin, L. and Shelley, W. B.: A Stain for Sweat Pore. *Nature 213:* 408, 1967.
14. Lewis, T.: *The Blood Vessels of the Human Skin and Their Responses.* Shaw & Sons, London, England, 1927.
15. Michaëlsson, G.: to be published.
16. Öberg, B. and Rosell, S.: Sympathetic Control of Consecutive Vascular Reactions in Canine Subcutaneous Adipose Tissue. *Acta physiol. scand. 71:* 47, 1967.
17. Rothman, S.: *Physiology and Biochemistry of the Skin. P. 90, Univ. Chicago Press,* Chicago Ill., 1954.
18. Solomon, L. M., Juhlin, L. and Kirschenbaum, M. B.: Prostaglandins on Cutaneous Vasculature. *J. Invest. Derm. 51:* 282, 1968.