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PRURITOGENIC ACTIVITY OF PROSTAGLANDIN E_2

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Abstract. The itch and erythematous responses induced by intradermal injection of histamine and PGE_2 were studied in human skin. Both compounds produced a sensation of itch. The histamine-elicited flare reached a maximum in 3 min and had disappeared after 1 hour. PGE_2 induced a similar flare reaction initially, but it was gradually replaced by a smaller, dusky and well delimited erythema. The itch and the flare-like erythema induced by either histamine or PGE_2 were alleviated when the subjects were pretreated with the antihistaminic drug chlorcyclizine, thus indicating that at least part of the PGE_2 response may be mediated via histamine release. However, when given combined in a mixture, histamine and PGE_2 elicited itch of longer duration and flare of larger area than could be accounted for by simple additive histamine effects. Thus, PGE_2 seems to potentiate the itch and flare responses induced by histamine in human skin.

Key words: Experimental itch; Histamine; Prostaglandin E_2; Histamine release; Potentiation

In dermatological practice pruritus is a common complaint. This symptom is often associated with inflammatory processes of the skin and for this reason potential inflammagens have been investigated for pruritogenic activity. Among them, histamine (2) and endopeptidases (18) elicit itch on intradermal injection and accordingly these agents have been implicated in the pathogenesis of itch.

The prostaglandins (PGs) constitute a class of biologically active, polyunsaturated C 20 hydroxy fatty acids present in most animal tissues including human skin (for reviews, see 7, 16, 23). Among their many biological actions the PGs seem to mediate some of the manifestations of the acute inflammatory response. This view is based on the findings of PG-like activity in exudates from various allergic and non-allergic types of inflammation (7) and on the fact that intracutaneous injection PGE_1 and PGE_2 produces wheal, erythema, hyperalgesia and pain (6, 13, 19, 20).

Whether PGs are pruritogenic or not is still a matter of debate. Some investigators claim that this is the case (3, 6), others state that PGs do not cause itch (19) or that they are not pruritogenic in themselves but lower the threshold of histamine-elicited itch (9). Since evidence exists of a histamine releasing effect of PGE_1 in human skin (20), any pruritogenic and/or potentiating effect of PGs could simply be held responsible for histamine release from the skin mast cells. In the present study we have tested this hypothesis by comparing the cutaneous responses elicited by histamine and PGE_2, injected alone and in combination, and by studying the effects of pretreatment with an antihistamine on the responses. PGE_2 was used since this PG is predominant in human skin (12, 22).

MATERIAL AND METHODS

The cutaneous responses, i.e. erythema and itch, were studied in healthy volunteers, aged 19–42 years. Some of the subjects took part in more than one of the experimental series. The same technique was used as previously described in studies on experimental itch (10, 11). Small volumes, 0.02 ml, of the solutions were injected intradermally on the lateral aspect of the upper arm. The area of the erythema was measured planimetrically after 3, 5, 20 and in some cases 60 min. The duration of the itch response was recorded.

The antihistamine chlorcyclizine and placebo tablets were given according to a double-blind cross-over

Table I. *Pruritogenic responses in 10 subjects given intradermal injections of PGE_2*

PGE_2 (μg)	Number of subjects perceiving itch	Itch duration mean ±S.E. (sec)
0[a]	0	0
0.02	4	23±12
0.1	7	49±12
0.5	10	159±52

[a] Buffered saline.

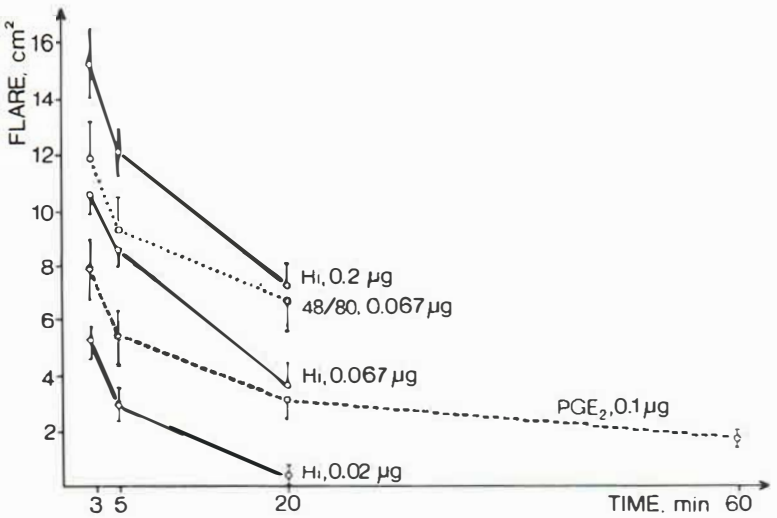

Fig. 1. Time course of flare reactions (mean±S.E.; $n=9$).

scheme. The subjects received three doses, one tablet at 3 p.m., one at 11 p.m. and one on the following morning 3 hours before test, i.e. at 7 a.m.

PGE_2 was kindly supplied by Dr J. Pike, Upjohn Co., Kalamazoo, Michigan, USA. It was stored in ethanol (1 mg/ml) at −20°C until use. Aliquots were taken on the day of each experiment and further diluted in saline buffered with phosphate buffer ($Na_2HPO_4+KH_2PO_4$, 6.7×10^{-3} M), pH 7.4. The highest ethanol concentration used in the experiments was 2.5% (v/v); on intradermal injections in control experiments this concentration of ethanol produced neither cutaneous effects per se nor inhibited the responses to histamine. Histamine hydrochloride and compound 48/80 were dissolved in the buffered salt solution. The histamine values quoted are expressed in terms of the salt. Compound 48/80 was a gift from Professor B. Högberg, AB Leo, Helsingborg, Sweden. Chlorcyclizine, 50 mg tablets (Di-paralene) and Di-paralene-placebo tablets were obtained by courtesy of Abbott, Belgium.

RESULTS

Cutaneous responses

Intracutaneous injection of PGE_2 produced a sensation of itch at the injection site. The number of subjects who felt itch increased with increasing concentration of PGE_2. In one series all 10 subjects experienced itch after injection of 0.5 μg of PGE_2, but only 4 of them did so after injection of 0.02 μg of PGE_2. Also the duration of the itch response was prolonged when the dose was increased (Table I). In all subjects, including those who could not feel itch at a low concentration of PGE_2, there was a rapidly developing erythema around the injection site. This reaction was similar to the flare that accompanied local injection of histamine. We therefore compared the erythematous responses induced by PGE_2 with those evoked by histamine and the histamine liberator compound 48/80 (Fig. 1). All compounds produced erythema of the flare type, appearing within one minute and with a maximum about 3 min after injection. The erythema then gradually subsided and 1 hour after the injection the histamine- and compound 48/80-induced reactions had disappeared. The PGE_2-induced response behaved differently. The initial bright red, fairly large, irregularly shaped flare gradually subsided and was replaced by a smaller, more dusky red and more well-delimited erythema, at the border of which a few projections resembling pseudopodia were observed.

Effect of an antihistamine on the cutaneous responses

From the above observations it seemed possible that at least some of the PGE_2-responses might be mediated by histamine. In order to investigate this aspect further, the effect on the PGE_2-induced responses of pretreatment with an antihistaminic drug, chlorcyclizine, was studied. In a cross-over designed experiment the subjects were given chlorcyclizine or placebo tablets; then PGE_2 (0.02, 0.1 and 0.5 μg) and histamine (0.02, 0.067 and 0.2 μg) were injected intracutaneously. Figs. 2 and 3 show that pretreatment with chlorcyclizine significantly reduced the flare and itch response to histamine as well as to PGE_2.

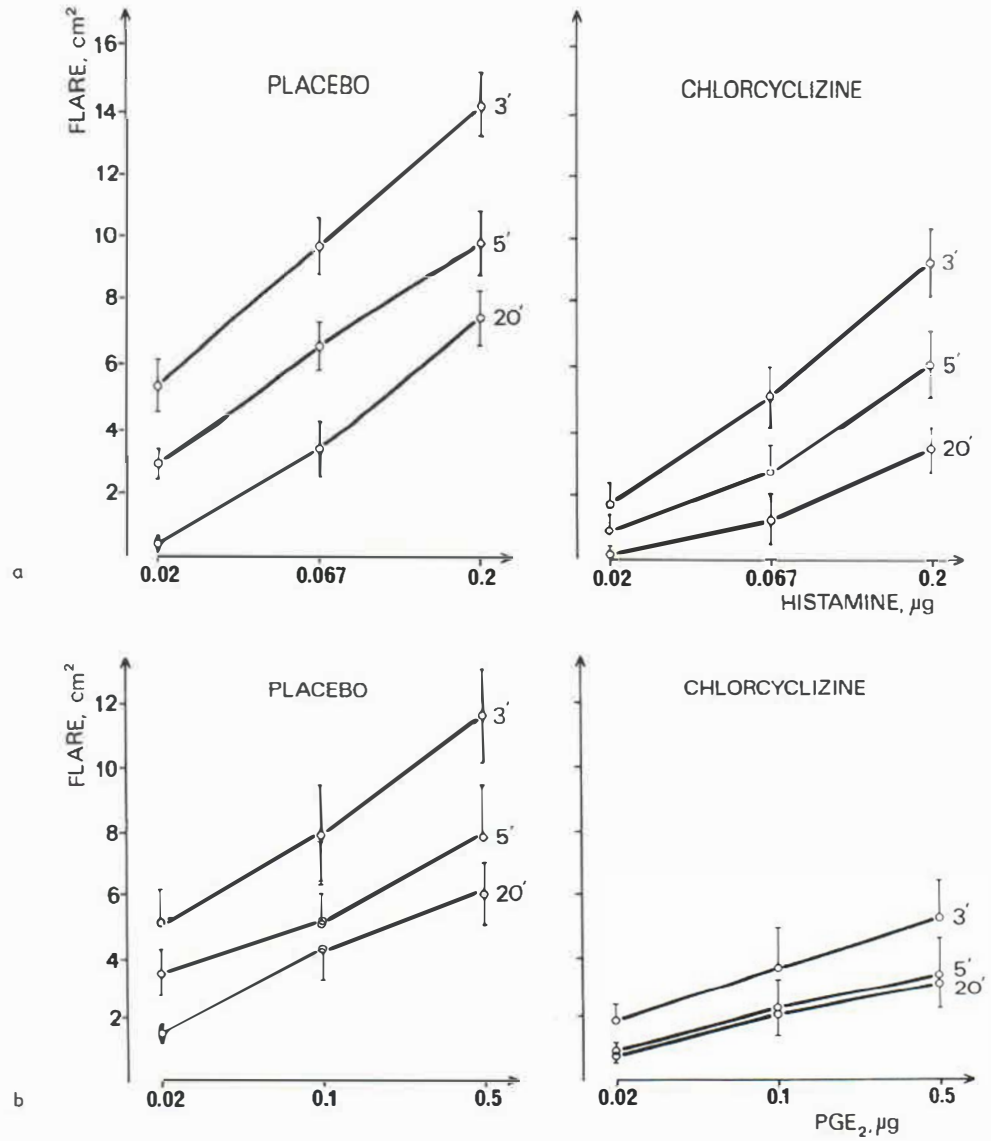

Fig. 2. Dose–response relations for histamine-induced (*a*) and PGE_2-induced (*b*) flare reactions after pretreatment with placebo and chlorcyclizine. The flare reactions were measured after 3, 5 and 20 min (mean ± S.E.; $n = 10$).

Effect of PGE_2 on the responses to histamine

In an attempt to examine whether PGE_2 potentiates the response to histamine the following experiment was carried out. In each of 9 subjects, histamine (0.02, 0.067 and 0.2 μg) and PGE_2 (0.02 and 0.1 μg) were injected separately. In addition, histamine (0.067 μg) was given together with PGE_2 (0.02 or 0.1 μg). The amounts of histamine required to produce responses equivalent to those evoked by PGE_2 and PGE_2 plus histamine respectively ("histamine equivalents") could then be calculated by intrapolation from the dose–response curves for histamine alone.

The individual data are shown in Table II. There was no synergistic effect of PGE_2 on the responses to histamine when the mixture of 0.02 μg of PGE_2 and histamine (0.067 μg) was given. On the other hand, when 0.1 μg of PGE_2 was given in combination with histamine (0.067 μg) 8 of the 9 subjects responded with longer duration of itch and a more marked flare reaction than was expected from additive histamine effects alone. The enhancing effect

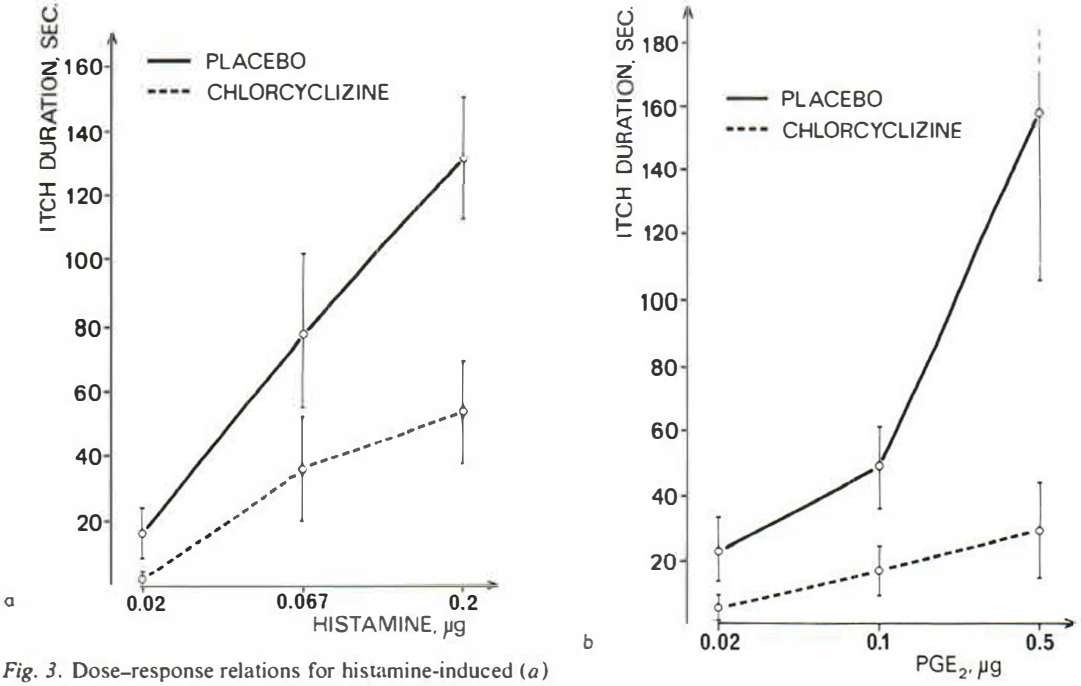

Fig. 3. Dose–response relations for histamine-induced (*a*) and PGE_2-induced (*b*) itch after pretreatment with placebo and chlorcylizine (mean± S.E.; $n=10$).

of PGE_2 on the responses to histamine was statistically significant ($p<0.02$). This is illustrated in Fig. 4 where the histamine equivalents for the mean responses to PGE_2 and to the mixtures of PGE_2 and histamine are presented. The values were calculated by intrapolation in the mean histamine dose-response curve for the 9 subjects. It is seen that 0.1 μg of PGE_2 produced itch of the same duration as would 0.05 μg of histamine and that more than 0.2 μg of histamine would be required to elicit itch of the same duration as that elicited by a mixture of 0.1 μg of PGE_2 and histamine (0.067 μg).

Table II. *Itch and flare induced by PGE_2 and PGE_2+histamine*

The responses are expressed as histamine equivalents, i.e. the amounts of histamine (in ng) calculated from the individual dose–response curves for histamine alone, giving the same itch and flare responses as actually obtained with PGE_2 and PGE_2+histamine. (+) denotes potentiation, i.e. the value is higher than expected from summation of the PGE_2 and histamine effects; (−) denotes lower value than expected from summation of the PGE_2 and histamine effects

Subject no.	PGE_2, 0.02 μg			PGE_2, 0.02 μg + histamine, 0.067 μg			PGE_2, 0.1 μg		
		Flare			Flare			Flare	
	Itch	3 min	5 min	Itch	3 min	5 min	Itch	3 min	5min
1	76	19	14	80 (−)	>200 (+)	>200 (+)	104	330	420
2	<20	27	25	154 (+)	>200 (+)	>200 (+)	<20	57	68
3	82	52	50	250 (+)	134 (+)	118 (−)	200	118	136
4	<20	11	18	124 (+)	184 (+)	95 (+)	136	134	37
5	98	70	62	86 (−)	106 (−)	140 (+)	68	98	68
6	70	23	23	70 (−)	96 (+)	44 (−)	70	80	40
7	<20	36	24	>200 (+)	180 (+)	162 (+)	44	58	50
8	12	12	<20	34 (−)	84 (+)	136 (+)	16	19	<20
9	<20	22	22	44 (−)	76 (−)	64 (−)	82	36	28
p-value[a]				>0.05	>0.05	>0.05			

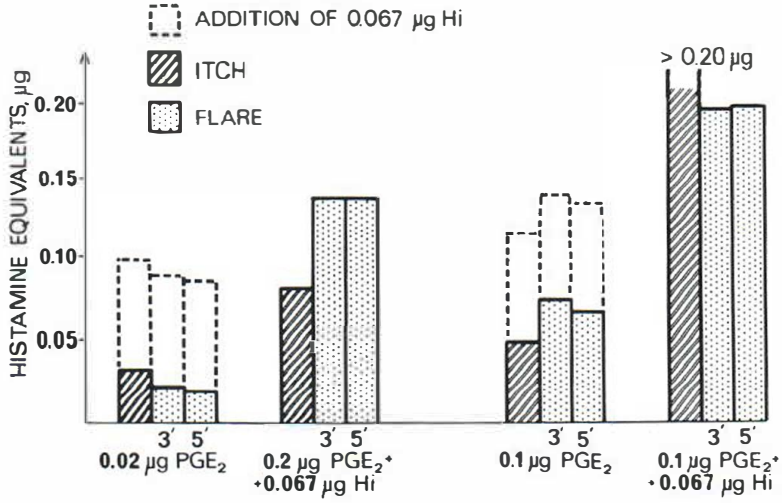

Fig. 4. Itch and flare induced by PGE_2 and PGE_2 + histamine in 9 subjects. Mean responses (solid columns) expressed as "histamine equivalents", i.e. the amounts of histamine calculated from the dose–response curves for histamine alone giving the same itch and flare responses as obtained with PGE_2 and PGE_2 + histamine. The superimposed (dotted extension) columns denote the addition of 0.067 µg of histamine to illustrate the effect of summation. The flare reactions were measured after 3 and 5 min.

DISCUSSION

In the present study PGE_2 caused itch on intradermal injection. The fact that some previous authors did not report itch (9, 19) might be due to their use of too small doses or too large injection volumes. In this study we observed that as much as 0.5 µg of PGE_2 was needed to elicit itch in all subjects. Furthermore, previous studies on experimental itch have emphasized the importance of injecting volumes smaller than 0.05 ml intradermally in order to avoid pressure effects blocking the itch response (18).

Histamine, PGE_2 and the histamine liberator compound 48/80 produced not only itch but also erythema. Irrespective of the compound injected, the erythema reached its maximum after 3 min, whereafter it gradually subsided. However, whereas the histamine- and compound 48/80-induced erythema disappeared completely within 1 hour, the PGE_2-induced erythema slowly became smaller, more sharply outlined and dusky. As has been observed by other investigators, it persisted for several hours (13, 19, 20). The early phase of the erythema as well as the pruritogenic response to either histamine or PGE_2 was reduced by pretreatment with the antihistamine chlorcyclizine, indicating that histamine is released as a consequence of the injection of PGE_2. It cannot be excluded, however, that part of the observed inhibiting effect of chlorcyclizine is due to vasoconstriction, since various antihistaminic compounds have been demonstrated to exert such an action on the microcirculation (1). In favour of a histamine releasing effect of PGE_2 is the finding that intradermal injection of PGE_1 reduces the histamine content of human skin (20). If PGEs release histamine, a direct

PGE_2, 0.1 µg +histamine, 0.067 µg

	Flare	
Itch	3 min	5 min
102 (−)	520 (+)	620 (+)
>200 (+)	200 (+)	>200 (+)
>200 (+)	>200 (+)	>200 (+)
212 (+)	>200 (+)	140 (+)
146 (+)	158 (−)	>200 (+)
>200 (+)	122 (−)	74 (−)
>200 (+)	190 (+)	184 (+)
122 (+)	184 (+)	180 (+)
>200 (+)	86 (−)	100 (+)
<0.02	>0.05	<0.02

effect on the tissue mast cells seems unlikely, since PGEs do not induce degranulation of rat mesenteric mast cells (14) or release histamine from isolated rat mast cells (Strandberg & Hägermark, unpublished). In other experimental systems, e.g. passive anaphylaxis in lung fragments and human basophils, PGEs even inhibit histamine release (15, 17).

Søndergaard & Greaves (20) found no effect of pretreatment with an antihistamine on the erythematous reaction to PGE_1 although the wheal was slightly suppressed. However, in their experiments the effect on the erythema was recorded 20 min after injection of PGE_1 and only a single peroral dose of the antihistamine was given, 1 hour prior to the experiment. In our study the antihistamine effect was most notable 3 and 5 min after injection of PGE_2, and we preferred to administer repeated doses of chlorcyclizine in order to ensure tissue distribution of the drug at the time of the experiment.

From the above discussion it follows that on injection of PGE_2 the initial phase of the erythema as well as part of the pruritogenic action may be produced by released histamine. In addition, PGE_2 seems to potentiate histamine-elicited itch, as proposed by Greaves & McDonald-Gibson (9). These authors applied gauze soaked in PGE_1 to a scarified area on the forearms for 30 min. This was followed by likewise application of increasing concentrations of histamine until itch occurred. In the concentration used (1 μg/ml), PGE_1 did not produce itch per se but lowered the threshold of histamine-evoked pruritus. Consequently, this effect was considered to reflect a true potentiating action of PGE_1. The possibility that histamine release by PGE_1 might contribute to the results was not commented upon, but it seems possible that continuous absorption of PGE_1 from the gauze may lead to a sustained release of histamine. Although the amounts of histamine released must be small—since PGE_1 by itself produced no itch—they might be sufficiently large to enhance the action of subsequently administered histamine.

In our analysis of the possible potentiating activity of PGEs we made an attempt to compensate for any histamine releasing action of PGE_2. To each test subject PGE_2, histamine and a mixture of the two were administered. By intrapolation in the dose–response curves for histamine, the activity of PGE_2 and of the mixture could be calculated in terms of "histamine equivalents". When comparing the histamine equivalents for PGE_2 (0.1 μg) injected alone with the data calculated for the mixture of PGE_2 (0.1 μg) plus histamine (0.067 μg) the responses caused by the mixture were more pronounced than could be fully accounted for by additive histamine effects. Thus, our findings agree with the concept that PGEs potentiate the actions of histamine in human skin. However, from our results we cannot distinguish whether PGE_2 only acts by sensitizing the tissue to histamine or if in fact the compound is a pruritogenic agent per se. In this context it may be noted that PGE_2 has been shown to potentiate the inflammatory responses to bradykinin and histamine in guinea-pig skin (21) and the vasoconstrictor effect of histamine in isolated kidney and lung (5). PGE_2 also increases the catecholamine-induced contraction of isolated human arteriolar muscle (8).

Regardless of the mechanism of the pruritogenic action of the PGEs, their effect can, to some extent, be counteracted by treatment with antihistamines. Since PGs are generated in inflammatory skin disorders there seems to be a rationale for the wide use of antihistaminic drugs in these conditions associated with pruritus.

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