

VASCULAR RESPONSES TO PROSTAGLANDIN E₁

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Abstract. The response of human cutaneous blood vessels to intradermal injection of prostaglandin E₁ was studied in order to evaluate the ability of this agent to cause the vascular changes seen in sustained acute inflammation of the skin. A single intradermal injection of 1 µg prostaglandin E₁ caused a persistent dusky erythema and a well-defined weal. Seven injections of 5 µg prostaglandin E₁ given intradermally at intervals of 8 hours resulted in a cutaneous reaction clinically characterized by redness, edema and tenderness. By using an arterial occlusion technique, the absence of tachyphylaxis with respect to wealing was demonstrated with prostaglandin E₁. Furthermore, absence of tachyphylaxis with respect to erythema formation was also demonstrated, since no reduction of the erythematous area occurred after repeated injections of prostaglandin E₁. This evidence suggests that prostaglandin E₁ can mediate vascular permeability in sustained acute inflammation.

The prostaglandins (PG) are a group of fatty acids, highly active in human skin (2, 6, 12). They have recently been suggested as possible causative agents of sustained cutaneous inflammation (5, 12). Prostaglandins and prostaglandin-like activity are released in cutaneous inflammatory reactions (1, 5, 10, 11). After repeated intradermal injections of PGE₁ the histological and biochemical changes were similar to those seen in early inflammatory reactions following tissue injury (14). However, in order to cause sustained acute inflammation, a vasoactive substance should not exhibit tachyphylaxis. The present study is concerned with experiments attempting to elucidate the still unsettled problem of tachyphylaxis of prostaglandin E₁ in human skin.

MATERIAL AND METHODS

Eighteen volunteer patients with localized non-inflammatory skin conditions not affecting the thighs and the arms were studied.

Prostaglandin E₁ dissolved in 0.154 M NaCl was injected intradermally. A volume of 0.1 ml was injected using a tuberculin syringe and a needle of 0.5 mm external diameter. The outlines of the resultant weal and erythema were traced on transparent paper and the areas measured planimetrically.

In order to demonstrate the presence or absence of tachyphylaxis in regard to wealing, the following method based on that of Lewis (9) as modified by Greaves & Shuster (3) was adopted. A sphygmomanometer cuff was placed on one upper arm of the patient and inflated above arterial pressure. One µg prostaglandin E₁ was injected intradermally when, because of arterial occlusion, no weal appeared. A control injection of the same dose of PGE₁ was performed on the opposite unoccluded forearm. Occlusion was terminated after 30 minutes, and 5 minutes later, 1 µg PGE₁ was injected into the precise site of the previous injection in both arms and the resulting weal was measured.

In order to demonstrate the presence or absence of tachyphylaxis with respect to erythema formation the following experiments were performed. Five µg PGE₁ was injected intradermally into the lateral aspect of the thigh. Each patient received 7 injections into the same site at intervals of 8 hours. Injections of 0.154 M NaCl were performed simultaneously on the opposite thigh for control. The resultant areas were measured planimetrically 60 minutes after each injection.

RESULTS

The presence or absence of tachyphylaxis in respect of weal response was determined in 8 subjects using the arterial occlusion technique. In each case, 1 µg PGE₁ was injected into a forearm, which had been rendered completely ischaemic. No weal appeared, although a faint erythema could be seen at the site of injection. Thirty minutes later the circulation was restored and after a further 5 minutes, no wealing could be detected at the site of the first injection in 3 subjects. In 5, a small weal developed, though smaller than the control weal. A second dose of 1 µg

Table I. Weal response to second dose of 1 µg prostaglandin E₁ injected at the same site as the first, 5 min after termination of arterial occlusion of 30 min duration

Injection of prostaglandin E ₁ 1 µg	Subject no.								Mean ± S.E. of responses for group (mm ²)
	1	2	3	4	5	6	7	8	
Control injection, no occlusion	100	105	70	90	90	70	70	30	78 ± 8
First injection, residual weal after termination of occlusion	5	10	0	20	15	0	20	0	
Second injection, reinjection at same site as first injection	105	100	55	95	120	80	85	70	—
Corrected response to second injection	100	90	55	75	105	80	65	70	80 ± 6

PGE₁ was then injected into the same site as the first and the resultant weal measured 5 minutes later. In all 8 subjects a weal appeared which was similar in size to the control weal (Table I). In the 8 subjects the mean area of the weals for the second injection of PGE₁ was 80 ± 6 mm² S.E. compared with 78 ± 8 mm² S.E. for the control injection. The differences between the means do not differ significantly ($p > 0.2$) indicating that tachyphylaxis in respect of weal formation was not caused by PGE₁.

Tachyphylaxis with respect to erythema formation was studied in 10 subjects each receiving seven intradermal injections of 5 µg PGE₁ at intervals of 8 hours. The ensuing reaction was characterized by redness, edema and tenderness

(Fig. 1). The erythema appeared almost immediately after the first injection and persisted for several hours. Eight hours after the first injection the erythema had diminished considerably in 8 of the 10 subjects and completely disappeared in 2. However, from the second injection and onwards the erythema persisted and did not disappear until 10–12 hours after the seventh injection. The difference in area between the erythema induced by the first and the subsequent injections of PGE₁ registered 60 minutes after the injections, did not differ significantly ($p > 0.2$) (Table II), indicating that tachyphylaxis in regard to erythema formation was not caused by PGE₁. Besides causing erythema, PGE₁ also

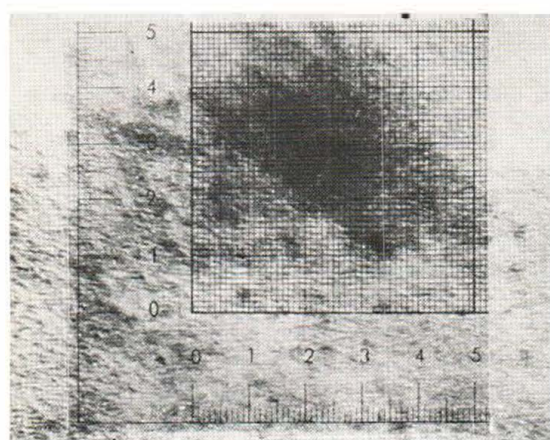


Fig. 1. Cutaneous reaction induced by seven intradermal injections of 5 µg PGE₁ given at intervals of 8 hours. The reaction is characterized by redness, edema and tenderness.

Table II. Erythema induced by repeated intradermal injections of 5 µg prostaglandin E₁

Each patient received 7 injections at intervals of 8 hours. The erythema was registered 60 min after each injection

Subject no.	Erythema (mm ²)	
	First injection	Seventh injection
1	1 365	1 440
2	590	625
3	995	790
4	730	1 040
5	770	895
6	570	1 010
7	695	425
8	640	945
9	490	1 070
10	485	590
Mean ± S.E.	733 85	883 92

produced a well-defined weal disappearing about 1 hour after the first injection. However, after the third injection of PGE_1 and onwards, although a slight profuse edema of the injected area was noticed (Fig. 1) no distinct weal was discernible. A slight tenderness of the injected area was experienced in each case after the second injection.

DISCUSSION

The technique of arterial occlusion used in the present study for testing for tachyphylaxis in regard to wealing is useful for evaluation of vasoactive substances. A clear distinction can be drawn between agents such as PGE_1 and histamine and serotonin. The latter two show tachyphylaxis (3) and therefore are likely to be capable of mediating only short-lived weal-and-flare reactions, i.e. local cutaneous anaphylaxis (13) and factitious urticaria (4). By contrast PGE_1 showed no evidence of tachyphylaxis, indicating that PGE_1 can cause sustained acute inflammation in the skin. The validity of the occlusion test depends on being able to show that the vasoactive agent is present during the period of ischaemia. This possibility does not require exploration since activity at the site of injection of PGE_1 after restoring the circulation was present in the form of a small weal in 5 and a faint erythema in all 8 subjects. The possibility remains, however, that vasoactivity persists after disappearance of PGE_1 .

The observation that repeated intradermal injections of PGE_1 did not cause tachyphylaxis in respect of erythema formation in human skin confirms and extends the findings of Juhlin & Michaëlsson (7). In 4 subjects they found that three intradermal injections of 0.1 and 1 μg of PGE_1 given at intervals of 24 hours produced exactly the same area of erythema each day. The disappearance of the well-defined weal observed by us after the third injection of PGE_1 may be due to the fact that the weal is caused, at least in part, by endogenous histamine release brought about by PGE_1 (12). However, this could not be demonstrated in the occlusion experiments.

Evidence is rapidly accumulating that the prostaglandins are implicated in inflammation (1, 5, 8, 10, 11, 14, 15). The results of the present study, which reveal that PGE_1 does not cause tachy-

phylaxis in human skin, support the view that PGE_1 can cause acute sustained cutaneous inflammation in man.

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