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SHORT REPORTS

Prostaglandin E_1 in Suction-separated Human Epidermal Tissue in Primary Irritant Dermatitis[1]

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Abstract. Experimental dermo-epidermal separation by suction was performed on primary irritant dermatitic and normal symmetrical skin areas. Primary irritant dermatitis was induced by 24-hour patch tests with an aqueous 10% benzalconium chloride solution in 12 healthy volunteers. PGE_1 activity in the epidermis, dermis and blister exudate was measured by a radioimmuno assay technique. The mean values in the epidermis (blister roof) was 1.57 ng/mg dry weight, dermis (blister base) 0.08 ng/mg dry weight and suction exudate (blister fluid) 1.61 ng/ml. The corresponding control values were: in epidermis 0.86 ng/mg dry weight, dermis 0.04 ng/ml dry weight and blister exudate 0.50 ng/ml. Thus significantly increased PGE_1 activity ($p<0.02$) was measured in the suction-separated samples in primary irritant dermatitis and furthermore, the highest level of PGE_1 activity was detected in epidermis.

Key words: Prostaglandin E_1; Primary irritant dermatitis; Epidermal–dermal suction separation

In primary irritant dermatitis most prostaglandin (PG) activity probably stems from epidermal synthesis and therefore therapeutic efforts should obviously be concentrated on substances acting at this level. So far, however, this has not been proved.

In previous studies on primary irritant dermatitis, whole-skin biopsies were examined (1) and PG synthesis was found to be increased. In skin perfusate of primary irritant dermatitis, PG activity was detected (2). Furthermore, fluid of suction bullae was found to contain increased amounts of PG (3). However, this is indirect evidence of epidermal PG synthesis.

[1] A brief account of this work was presented at the ESDR meeting, Amsterdam, May, 1980.

In this study, the suction technique for epidermal–dermal separation, described and microscopically evaluated by Kiistala & Mustakallio (4, 5, 6), has been used to obtain epidermal tissue for PG investigation. The aim was to evaluate PG synthesis in primary irritant dermatitis of human epidermal tissue (the blister roof). In addition, blister fluid and dermal tissue from some of these patients were examined.

MATERIAL AND METHOD

Patients

Primary irritant dermatitis was induced on the abdomen of 12 subjects by 24-hour patch tests with an aqueous 10% benzalconium chloride solution, and the findings were compared with those obtained in a symmetrical control area of uninvolved skin of the same 12 subjects. Erythema, infiltration and vesicles was assessed by the investigator. The patients had not previously been exposed to benzalconium chloride. All subjects were volunteer patients with venous leg ulcers but no other skin diseases. Further clinical data are shown in Table 1.

Suction and sampling

Plastic suction cups (5 cm diameter) with an inside adapter plate with five holes, each having a diameter of 6 mm, were applied to the areas (6 cm^2) of positive patch test 24 hours after application of the patch, and symmetrically on the clinically normal skin of the abdomen. Suction pressure was 300 mmHg below atmospheric pressure.

Table 1. *Degree of inflammation before suction (clinical data)*

−=no clinical reaction, +=weak, ++=medium strong, +++=strong

Subject	Age/sex	Erythema	Infiltration	Vesicles
1	53/F	+	+	−
2	57/M	++	++	−
3	60/M	+++	+++	+
4	72/M	++	++	−
5	75/M	+++	+++	+++
6	75/F	+	+	−
7	66/F	++	++	−
8	58/F	++	++	−
9	69/F	+++	+++	+
10	60/F	++	++	−
11	61/M	+	+	−
12	62/M	++	+++	+

Table II. *Prostaglandin E_1 activity*

Subject	Primary irritant dermatitis			Controls		
	Epidermis (ng/mg dry wt)	Dermis (ng/mg dry wt)	Blister fluid (ng/ml)	Epidermis (ng/mg dry wt)	Dermis (ng/mg) dry wt)	Blister fluid (ng/ml)
1	0.62	0.03	0.08	0.25	0.02	0.03
2	0.72	0.04	0.83	0.30	0.02	0.16
3	0.94	0.05	0.30	0.35	0.02	0
4	0.63	0.02	0.07	0.18	0.01	0.05
5	0.46	0.14	2.70	0.30	0.02	1.05
6	2.15	0.19	5.70	1.60	0.12	1.23
7	1.39			0.30		
8	2.02			1.26		
9	0.28			0.08		
10	1.43			0.41		
11	6.61			5.10		
12	1.54			0.22		
Mean values	1.57	0.08	1.61	0.86	0.04	0.50

Suction was discontinued when the first blister became visible through the window of the suction cup. The required suction time (separation time) averaged 65 min on the inflamed and 95 min on the normal skin.

From 6 of the patients, the blister fluid was aspirated, the epidermal tissue of all the blisters was removed and dermal specimens obtained by 6 mm punch biopsy from the blister base. The sampling was carefully performed, avoiding unnecessary trauma and bleeding. All the samples were immediately frozen in liquid nitrogen and stored at −80°C.

Prostaglandin measurement

A detailed account of the method of PG extraction and assay has been presented elsewhere (7). In all experiments, extraction was done with ethyl acetate after homogenization and acidification of the samples. PGE_1 was converted to PGB_1 by alkalization with NaOH before entering the radioimmunoassay.

RESULTS

All 12 subjects developed a primary irritant reaction to benzalconium chloride. The degree of inflammation recorded as erythema, infiltration and vesiculation is presented in Table I. The PGE_1 levels of the epidermal, dermal and blister fluid samples were detected by radioimmunoassay. As a whole, samples from the benzalconium chloride treated areas showed significantly higher PGE_1 activity ($p<0.02$) than those from the suction-separated, clinically normal epidermis (Table II).

The highest levels of PGE_1 activity in the skin of primary irritant dermatitis were detected in the epidermal samples (1.57 ng/mg dry weight). In contrast, the inflamed dermal samples contained 0.08 ng/mg dry weight, and the blister fluid 1.61 ng/ml of PGE_1. The corresponding control values were 0.86, 0.04 and 0.50, respectively (Table II).

DISCUSSION

Epidermal synthesis is the main source of PG activity in normal skin, whereas the dermal cells are usually minor contributors (10). Previously it has been reported that PG levels are elevated in whole-skin biopsies and in suction blister fluid from patients with primary irritant dermatitis (1, 2, 8, 9). In this study we have demonstrated that in human skin in primary irritant dermatitis the highest level of PGE_1 activity is found in the epidermis (Table II). Since PGs are not stored in tissues this would indicate an increased biosynthesis by epidermal tissue. An inflammatory cutaneous stimulus such as benzalconium chloride produces a cellular infiltrate in the upper dermis, initially consisting mainly of polymorphonuclear leukocytes.

Leukocytes are known to produce and release PG when they migrate into an inflammatory focus (11, 12). In addition, lysosomal enzymes released from leukocytes or macrophages may induce PG production from neighbouring dermal and epidermal cells. Although we found some increased PG activity in the inflamed dermal tissue mirrored in the blister fluid, which could stem from invading leukocytes and activation of dermal cells, the highest PG activity was detected in the epidermis. It is uncertain whether this increased epidermal activity stems from the inflammatory stimulus itself by a direct

action on epidermal cell membranes or is indirectly evoked by the invading inflammatory cells. Some of the arachidonic acid cascade metabolites have chemotactic activities and others, including PGE_1, may modulate the chemotactic response (13). The increased PGE_1 formation by epidermal tissue might be an essential contribution to the development and persistence of primary irritant dermatitis. Therapeutic attempts to regulate PG formation in inflammatory skin conditions such as primary irritant dermatitis should therefore be made to control epidermal PG synthesis.

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REFERENCES

1. Jørgensen, H. P. & Søndergaard, J.: Biosynthesis of prostaglandins by human inflamed skin. Acta Dermatovener (Stockholm) *56:* 11, 1976.
2. Søndergaard, J., Greaves, M. W. & Jørgensen, H. P.: Recovery of prostaglandins in human primary irritant dermatitis. Arch Dermatol *110:* 556, 1974.
3. Black, K. A., Greaves, M. W., Hensby, C. N., Plummer, N. A. & Eady, R. A. J.: A new method for recovery of exudates from normal and inflamed human skin. Clin Exp Dermatol *2:* 209, 1977.
4. Kiistala, U. & Mustakallio, K. K.: In vivo separation of epidermis by production of suction blisters. Lancet *i:* 1444, 1964.
5. Kiistala, U.: Suction blister device for separation of viable epidermis from dermis. J Invest Dermatol *50:* 129, 1968.
6. Kiistala, U. & Mustakallio, K. K.: Dermo-epidermal separation with suction. Electron microscopic and histochemical study of initial events of blistering on human skin. J Invest Dermatol *48:* 466, 1977.
7. Kassis, V. & Søndergaard, J.: Determination of prostaglandin E_1 in heat separated epidermal tissue. IRCS Medical Science *7:* 101, 1979.
8. Goldyne, M. E.: Prostaglandins and cutaneous inflammation. J Invest Dermatol *64:* 377, 1975.
9. Black, A., Heinsby, C. & Greaves, M. W.: The pharmacological effects of systemic steroids on arachidonic acid and prostaglandins on human cutaneous inflammation. ESDR meeting, Amsterdam, May 1980, p. 9.
10. Van Dorp, D.: Recept developments in the biosynthesis and the analyses of prostaglandins. Ann NY Acad Sci *180:* 181, 1971.
11. Di, Rosa, M. & Willoughby, D. A.: Screens for anti-inflammatory drugs (Letter to the Editor). J Pharm Pharmacol *23:* 297, 1971.
12. Higgs, G. A. & Youlten, L. J. F.: Prostaglandin production by rabbit peritoneal polymorphonuclear leukocytes in vitro (abstr.). Br J Pharmacol *44:* 330 P, 1972.
13. Flower, P. J.: Drugs which inhibit prostaglandin biosynthesis. Pharmacol Rev *26:* 33, 1974.

Androgen Abnormalities in Acne Vulgaris

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Abstract. Thirty-six women with acne vulgaris who consulted gynecologist with complaints of hirsutism, infertility, menorrhagia, or oligomenorrhea were evaluated for an androgen abnormality with assays for testosterone (T), androstenedione (A), and dehydro-epi-androsterone (DHEA). Forty-eight percent of the DHEA measurements were elevated and 61% of the patients had elevation of one or more of the three measurements. The frequency of abnormal androgen levels remained relatively constant regardless of the severity of the presenting signs and symptoms. This study calls attention to the high frequency of an androgen abnormality in acne patients who also have evidence of hirsutism, menstrual irregularity, and/or infertility. Consideration should be given to assaying DHEA, T, and A levels in an effort to discover those patients who have a systemic endocrine disorder, of which acne manifests as a sign.

Key words: Acne; Androgens; Hirsutism; Infertility; Oligomenorrhea

Acne vulgaris, the multifactoral dermatologic disorder of the pilosebaceous apparatus, is a common entity frequently affecting adolescents and young adults. Androgenic stimulation of the sebaceous glands has been implicated as a major etiological factor in the pathogenesis of the entity (3).

It has been shown that sebum production by the sebaceous gland is stimulated by androgens, primarily testosterone and its metabolite dihydrotestosterone (DHT) (1). Some studies have implied that excessive levels of androgens in the skin are contributory to the lesions of acne, as androgens stimulate the mitotic activity in the sebaceous glands, fibroblasts, and hair follicles, resulting in obstruction of the pilosebaceous unit (7).