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Psoriasis and Endothelins

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Background: Psoriasis is characterized by an abnormal proliferation and increased turnover of keratinocytes, the presence of acute and chronic inflammatory cells and microangiopathic changes. Endothelins are a family of peptides which have been investigated especially for their effects on the cardiovascular system. Recent studies have demonstrated their involvement also in human skin.

Aim of the study: We evaluated the Endothelin-1 and 2 plasma levels in psoriatic patients, as endothelin-1 can be produced in vitro by keratinocytes and can stimulate the proliferation of fibroblasts as well as modify the skin microcirculation dynamics.

Patients and methods: We studied 30 patients: 10 affected with psoriasis (PASI from 5 to 10), 10 affected with cardiovascular diseases and 10 healthy controls. The Endothelin-1 and 2 plasma levels were evaluated by radio-immunoassay procedure.

Results: A significant increase in Endothelin-1 and 2 plasma levels was observed in the psoriatic patients, in comparison with the controls.

Conclusions: Our data seem to suggest a possible relationship between psoriasis and increased plasma level of endothelin-1 and 2, though the possible role played in the pathogenesis of psoriasis needs further studies. ***Key words: psoriasis, endothelins.***

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The endothelins (ETs) are a family of recently discovered 21 aminoacid peptides (1). In Man, ETs occur in the isoform ET-1, ET-2 and ET-3, after a proteolytic processing of the specific preproendothelin (1). Yohn et al. (2) have recently found that human keratinocytes are able to synthesize and secrete ET-1 in vitro. Macrophages (3), monocytes (3) and astrocytes (4) can also secrete ET-1. Many human cancer cell lines, including those from human colon and liver, can produce ETs (5). ET-1 is the most powerful vasconstrictor substance known.

These properties suggest that ET plasma levels could vary in psoriasis, a pathology characterized by abnormal proliferation and increased turnover of keratinocytes, the presence of acute and chronic inflammatory cells and microangiophatic changes. In the present study we evaluated ET-1 and 2 plasma levels in 10 psoriatic patients and in two control groups.

PATIENTS, MATERIALS AND METHODS

Ten patients (5 males and 5 females, range: 38–77 years mean age: 60.9 years) affected with psoriasis (PASI from 5 to 10) were compared with two control groups: 10 patients affected with cardiovascular diseases (hypertension or ischaemic cardiopathy) and 10 healthy subjects comparable for age and sex.

A blood sample was taken from each of them, between 7.30 and 9.30 a.m., from the antecubital vein without blood stasis, after the subject had rested supine for 10 min.

The blood samples, collected with a 19 G neddle and mixed in Vacutainer tubes with 7.5 mM ETDA (13:1), were immediately placed in melting ice. The samples were centrifuged within 1 hour at 2,000 *g* for 10 min in a refrigerated centrifuge (4°C). Plasma aliquots were frozen at −70°C until assay.

An extraction procedure of ETs from plasma was performed before analysis. After thawing, 1 ml plasma was acidified using 0.25 ml 2 M HCl and centrifuged at 10,000 *g* for 5 min at room temperature.

1 ml of surnatant was charged on an Amersham C2 column (500 mg) (Amersham, Bucks, England) previously conditioned by washing with 2 ml methanol followed by 2 ml water. The column was rinsed with 5 ml water + 0.1% trifluoroacetic acid. The eluate was collected after washing the column with 2 ml 80% acetonitrile in water + 0.1% trifluoroacetic acid in a polypropylene tube. All the washing procedures were performed with a VACELUT vacuum system (Analitichem International) maintaining the flow rate below 5 ml/min. The eluate was dried under vacuum and reconstitued in 250 µl of assay buffer for R.I.A. ET-1 and 2 (high sensitivity) assay system with magnetic separator (Amersham).

STATISTICAL METHODS

The Wilcoxon test was employed to compare the three groups.

RESULTS

Psoriatic patients showed a significant increase in ET-1 and 2 plasma concentration (6.4 + 1.9 pg/ml) in comparison with both the patients with cardiovascular diseases and the normal subjects ($p = 0.0274$ v. cardiovascular patients; $p = 0.0357$ v. normal subjects) (Fig. 1). The two control groups did not show any significant difference when compared with each other (4.8 + 0.8 pg/ml v. 4.7 + 1.3 pg/ml, $p = 0.8336$).

DISCUSSION

A marked vascular and lymphatic dilatation and increased blood flow (twice the normal) appeared at the site of the psoriatic lesions (6, 7). The capillary loops of the lesional dermal papillae were dilated and tortuous (8). These microcirculation changes were present before psoriatic skin lesions appeared (7, 9).

Endothelins (ETs) were isolated from supernatant of cultured porcine aortic endothelial cells by Yanagisawa et al. (10) in 1988. They act via cell surface receptors, whose binding is rapid, specific and saturable (11).

Hitherto, ETs are the most powerful vasoconstrictor substances known. ET-1 induces strong and long-lasting constrictor effects in microvessels. It also causes bronchoconstriction (12), inhibits renin release from juxtaglomerular cells (13, 14), modulates autonomic transmission (15) and exerts positive inotropic and chronotropic effects on the myocardium (16, 17, 18, 19). By contrast, the activities of ET-2 and ET-3 have not hitherto been well defined.

ETs are mitogenic for vascular smooth muscle cells (20), fibroblasts (21) and renal mesangial cells (13, 22). Specific

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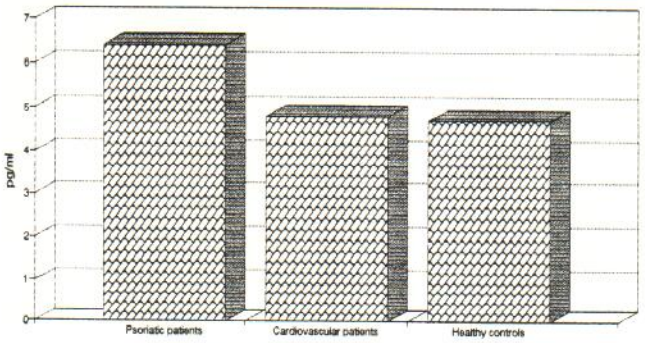

Fig. 1. ET-1,2 plasma levels.

high-affinity receptors for ET-1 have been identified in melanocytes and in fact ET-1 stimulates melanocyte proliferation and tyrosinase activity (2).

5 pmol/l of ET-1 has been determined in human plasma (23), thus suggesting that there is a basic physiological secretion. Numerous agents and several mechanical stimuli enhance *de novo* synthesis of ET-1. Many investigators have reported that thrombin, transforming growth factor β (TGβ), angiotensin II, ephineprine, arginine vasopressin, bradykinin, interleukin 1, calcium ionophore A 23187, inomycin, phorbol esters, and hypoxia all increase the expression of the preproendothelin gene or the ET-1 release (1, 10, 24).

ET-1 is clearly implicated in Raynaud's phenomenon; in this pathology an increase in the plasma ET-1 levels is observed and the cold challenge of an arm leads to a pronounced ipsilateral increase in plasma ET-1 (25).

In this paper we have described a significant increase in plasma levels of ET-1 and 2 in psoriatic patients, compared with two control groups. In our opinion these data are quite unexpected in view of the known vasoconstrictor properties of ETs and could perhaps be considered an epiphenomenon of the alterations observed in psoriasis. Moreover, we recall that some authors emphasize that ETs have a dose-related action on vessel resistance: little vasodilator effect at low doses and marked vasoconstriction at higher doses (19).

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REFERENCES

1. Caputi AP, Squadrito F, Zingarelli B. Vasocostrittori di origine endoteliale: le endoteline. In: Dejena E, Prosdocimi M, eds. Il laboratorio endoteliale. Rome: Il Pensiero Scientifico Editore, 1991; 25–50.
2. Yohn JJ, Morelli JG, Walchak SJ, Rundell KB, Norris DA, Zamora MR. Cultured human keratinocytes synthesize and secrete endothelin-1. J Inv Dermatol 1993; 100: 23–26.
3. Ehrenreich H, Anderson RW, Fox CH, Rieckmann P, Hofman GS, Travis WD, Coligan JE, Kehrl JE, Fauci AS. Endothelins, peptides with potent vasoactive properties, are produced by human macrophages. J Exp Med 1990; 172: 1741–1748.
4. Supattapone S, Simpson AWM, Ashley CC. Free calcium rise and mitogenesis in glial cells caused by endothelin. Biochem Biophy Res Commun 1989; 165: 1115–1122.
5. Ishibashi M, Fujita M, Nagai K, Kako M, Haku E, Osamura Y, Yamaji T. Production and secretion of endothelin by hepatocellular carcinoma. J Clin Endocrinol Metab 1993; 76: 378–783.
6. Nyfors A, Rothenborg HW. Cutaneous blood flow in psoriasis measured by 133 Xenon clearance. J Invest Dermatol. 1970; 54: 381–385.
7. Braverman IM, Yen A. Microcirculation in psoriatic skin. J Invest Dermatol 1972; 59: 91–98.
8. Telner P, Fekete Z. The capillary responses in psoriatic skin. J Invest Dermatol 1961; 36: 225–230.
9. Kulka JP. Microcirculatory impairment as a factor in inflammatory tissue damage. Ann NY Acad Sci 1964; 116: 1018–1044.
10. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yazaki Y, Goto K, Masaki T. A novel potent vasoconscrictor peptide produced by vascular endothelial cells. Nature 1988; 332: 411–415.
11. Simonson MS, Dunn MJ. Cellular signaling by peptides of the endothelin gene family. Faseb J 1990; 4: 2989–3000.
12. Uchida Y, Ninomiya H, Saotome M, Nomura A, Ohtsuka M, Yanagisava M, Goto K, Masaki T, Hasegawa S. Endothelin, a novel vasoconstrictor peptide, as potent bronchoconstrictor. Eur J Pharmacol 1988; 154: 227.
13. Perico N, Remuzzi G. Vascular endothelin and renal disease progression. Contrib Nephrol 1992; 100: 236–253.
14. Takagi M, Matsuoka H, Atarashi K, Yagi S. Endothelin: a new inhibitor of renin release. Biochem Biophys Res Commun 1988; 157: 1164–1168.
15. Wiklund NP, Ohlen A, Cederqvist B. Inhibition of adrenergic neuroeffector transmission by endothelin in the guinea-pig femoral artery. Acta Physiol Scand 1988; 134: 311–312.
16. Gu X-H, Casley D, Nayler W. Specific high affinity binding sites for I-labelled porcine endothelin in rat cardiac membranes. Eur J Pharmacol 1989; 167: 281–290.
17. Gu X-H, Casley DJ, Cincotta M, Nayler W. I-endothelin-1 binding to brain and cardiac membranes from normotensive and spontaneously hypertensive rats. Eur J Pharmacol 1990; 177: 205–209.
18. Ishikawa T, Yanagisawa M, Kimura S, Goto K, Masaki T. Positive inotropic action of a novel vasoconstrictor peptide endothelin on guinea pig atria. Am J Physiol 1988, 255: 970–978.
19. Kiowski W, Luscher TF, Linder L, Buhler FR. Endothelin-1-induced vasoconstriction in humans. Reversal by calcium channel blockade but not by nitrovasodilators or endothelium-derived relaxing factor. Circulation 1991; 83: 469–475.
20. Koide M, Kawahara Y, Tsuda T, Ishida Y, Shu K, Yokoyama M. Endothelin-1-stimulates tyrosine phosphorylation and the activities of two mitogen-activated protein kinases in cultured vascular smooth muscle cells. J Hypertens 1992; 10: 1173–1182.
21. Falanga V, Katz MH, Kirsner R, Alvarez AF. The effects of endothelin-1 on human dermal fibroblast growth and synthetic activity. J Surg Res 1992; 53: 515–519.
22. Simonson MS, Wann S, Mene P, Dubyak GR, Kester M, Nakazato Y, Sedor J, Dunn MJ. Endothelin stimulates phospholipase C, Na/H exchange, c-fos expression and mitogenesis in rat mesangial cells. J Clin Invest 1989; 83: 708–712.
23. Davenport AP, Ashby MJ, Easton P. A sensitive radioimmunoassay measuring endothelin-like immunoreactivity in human plasma: a comparison of levels in patients with essential hypertension and normotensive control subject. Clin Sci 1990; 78: 261–264.
24. Bull HA, Dowd PM. Endothelin-1 in human skin. Dermatology 1993; 187: 1–5.
25. Zamora MR, O'Brien RF, Rutherford RB, Weil JV. Serum endothelin-1 concentrations and cold provocation in primary Raynaud's phenomenon. Lancet 1990; i: 1144–1147.