ADRENORECEPTOR BLOCKADE: MECHANISM OF DISTURBANCE OF HUMORAL-CELLULAR REGULATION OF EPIDERMOCYTE PROLIFERATION IN PSORIASIS

I. M. Raznatovskii, E. V. Khvatov, and V. Ya. Egorov

UDC 616.517-07:616.591-018.15-092:616.45-008.64-092.9

KEY WORDS: Psoriasis; adrenoreceptors; epidermocytes; regulation of proliferation.

The nature, role, and mechanisms of action of humoral factors in the tissue-specific regulation of epidermocyte proliferation under normal and pathological conditons and, in particular, in a dermatosis so widespread as psoriasis, still remain largely unstudied. Information on these questions consists only of isolated facts.

The blood serum from patients with psoriasis has been shown to potentiate epidermocyte proliferation, by blocking the biological effect of epidermal chalones [4, 9]. This ability is most marked in the progressive stage of the disease [9] and is reduced after these patients have undergone hemoperfusion [8]. Relapses and aggravation of the course of psoriasis described by clinicians in patients treated with β-adrenoblockers for concomitant diseases [15, 16, 22], suggest that potentiation of epidermocyte proliferation is due to the influence of substances acting selectively on β-adrenergic receptors of cell membranes. The possibility that chalones, including epidermal, may realize their biological effect through interaction with membrane β-adrenoreceptors is accepted by several workers [14, 21]. As regards the nature of the blood serum component of components of psoriasis patients that participate in the regulation of epidermocyte proliferation and exert an antichalone action, they may be found among compounds with average or low molecular weight (under 2000 daltons), an increased concentration of which in the blood serum of psoriasis patients has been demonstrated biochemically [10, 18, 19]. The view has been expressed [9] that disturbance of epidermocyte proliferation in psoriasis may be connected with competitive interactions of unknown components, appearing in the blood serum of patients with this dermatosis, and epidermal chalones, for membrane receptors.

The aim of this investigation was to verify experimentally the presence of such components in the blood serum of psoriasis patients.

EXPERIMENTAL METHODS

A technique of recording spontaneous contractile activity of smooth-muscle cells of the portal vein, by means of which the effect of various biologically active substances, whose action is mediated through the membrane receptor apparatus can be studied, was used. The investigation was conducted on the portal vein of healthy, mature Wistar rats. After decapitation and laparotomy, a region of the portal vein about 10 mm long was excised, and transferred on ligatures, applied to the polar regions of the excised segment of the vessel, into the perfused cell of a thermostatically controlled working chamber. One end was fixed securely, the second connected to the moving leg of the tube of a 6MXIC mechanotron. The preparation was stretched by a measured amount with a force of 200 mg. Spontaneous contractile activity was recorded by means of an H-327-I high-speed automatic ink writer. Aerated Krebs' physiological saline for blood vessels, at a temperature of 34°C, maintained by a UR-1 ultrathermostat, was used for perfusion. The substances for testing were added directly to the perfusion solution after adaptation of the preparation to the conditions of the perfused cell for 30 min. The effect of the following substances on spontaneous contractile activity of the myocytes of the portal vain was studied: 1) ultrafiltrate of blood serum from a

Department of Dermatovenereology, I. P. Pavlov First Leningrad Medical Institute. A. I. Gertsen Leningrad State Pedagogic Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR O. K. Shaposhnikov.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 105, No. 4, pp. 488-491, April, 1988. Original article submitted March 31, 1987.

TABLE 1. Effect of Blood Serum from Healthy Donors and from Psoriasis Patients and of Propranolol on APC (M ± m)

Test substance	Initial amplitude, mg	Amplitude after addition of substance, mg
Ultrafiltrate of blood serum from healthy donor	98,2142±7,2749	99,3103±7,8459[1]*
	149,375±20,1136	151,7647±12,2545[1]*
	78,5±5,8613	78,5714±3,8597[1]*
	66,5±2,9267	68,1818±4,7279[1]*
	111,0526±8,681	109,0909±5,6948[1]*
	262,1052±17,3639	258,1818±11,3891[1]*
	98,5±5,8613	98,571±3,86[1]*
	86,5±2,927	88,182±4,728[1]*
	169,375±20,1136	171,7647±12,2545[1]*
	119,0476±5,602	118,1818±3,5818[1]*
	107,619±3,0003	109,5622±4,7664[1]*
	100%	100,5987%
Ultrafiltrate of blood serum from psoriasis patient before hemoperfusion	103,6363±0,8651	132,7272±9,629[2]*
	117,1428±9,6321	220±14,2488[5]*
	104,375±13,6311	188±8,0[5]*
	80±5,8983	99,5±5,7799[2]*
	58,9473±3,5782	70,4761±3,8715[2]*
	97,826±4,8273	139,5454±7,1917[5]*
	113±11,7002	160±15,0632[3]*
	261,1111±22,3766	375,6531±21,6678[5]*
	224±17,4476	307±21,3381[4]*
	242±18,5755	358,9473±33,5248[4]*
	105,9259±7,6284	145,7144±3,6234[5]*
	137,1428±9,6321	240±14,2488[5]*
	124,375±13,6314	208±8,01[5]*
	100±5,8298	119,5±5,78[2]*
	122,1739±5,5864	159,5454±7,1920[5]*
	264,01±17,447	347±21,34[4]*
	100%	146,5845%
Ultrafiltrate of blood serum from psoriasis patient after hemoperfusion	84±5,9116	86,4705±5,8120[1]*
	86,9565±5,2387	86,8965±4,3860[1]*
	62,8671±4,5001	71,7647±4,2213[1]*
	132,7777±9,3167	124,7619±11,4563[1]*
	106,9565±5,24	106,896±4,28[1]*
	152,2222±9,4226	144,7620±11,456[1]*
	100%	101,0076%
Propranolol	105±12,9976	183,3333±22,9734[4]*
	83,6±3,6914	113,6363±4,2408[5]*
	215,01±20,0459	291,7647±16,4548[4]*
	125,02±12,99	203,3±22,9[4]*
	255±20,05	331,76±16,46[4]*
	100%	147,8013%

Legend. Significance of differences compared with initial amplitude: [1]*$P < 0.05$, [2]*$P < 0.05$, [3]*$P < 0.02$, [4]*$P < 0.01$, [5]*$P < 0.001$.

healthy donor in a concentration of 20 vol. %; 2) ultrafiltrate of blood serum from a patient with psoriasis in the progressive stage of the cutaneous eruptions, before hemoperfursion, in the same concentration; 3) an ultrafiltrate of blood serum from a patient with psoriasis after hemoperfusion, in the same concentration; 4) the β-blocker propranolol (Sigma, USA) in a concentration of 100 ng/ml. The patient's blood was taken immediately before hemoperfusion and immediately after the end of the procedure. Ultrafiltration of the serum was carried out through "Ripor-4-64" membranes in the FM-02 apparatus, under nitrogen with a pressure of 0.3 MPa, whereby an ultrafiltrate of serum containing components with mol. wt. of below 2000 daltons could be obtained. The indicator of the effect of the test substances was a change in the most informative parameter, namely the amplitude of phasic contractions (APC). The results were expressed in milligrams. During analysis of the absolute values of APC, arithmetic mean values were calculated. To analyze the time course of individual values of APC, Student's t test was used.

EXPERIMENTAL RESULTS

Addition of ultrafiltrate of blood serum from a healthy donor to the perfusion solution caused no significant changes in APC (Table 1, Fig. 1a). Addition of the blood serum ultra-

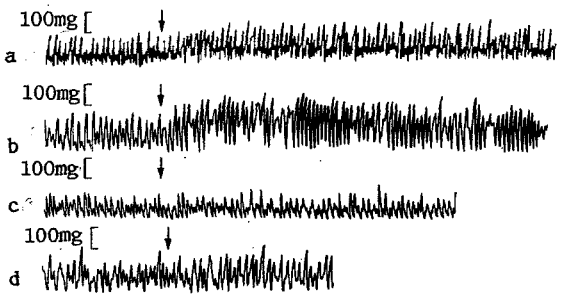

Fig. 1

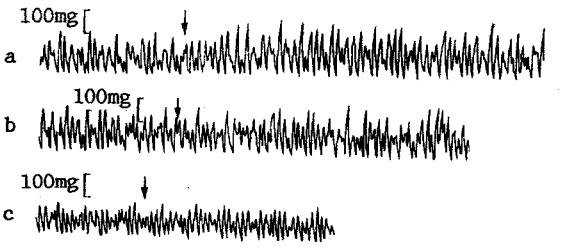

Fig. 2

Fig. 1. Changes in spontaneous contractile activity of portal vein myocytes under the influence of blood serum ultrafiltrate from a healthy donor (a), a psoriasis patients before hemoperfusion (b), and after hemoperfusion (c), and of propranolol (d).

Fig. 2. Changes in spontaneous contractile activity of portal vein myocytes under the influence of blood serum ultrafiltrate from psoriasis patient before hemoperfusion (a), and of propranolol preceded by the action of blood serum ultrafiltrate from psoriasis patients before (b) and after (c) hemoperfusion.

filtrate from a patients with psoriasis before hemoperfusion led to a significant ($p < 0.05$) increase in the APC of the portal vein myocytes (Table 1; Figs. 1b and 2a) by 46.5%. In the corresponding investigation of the effect of blood serum from a psoriasis patient after hemoperfusion, no significant changes were found in APC (Table 1; Fig. 1c). Addition of propranolol to the perfusion solution caused a significant ($p < 0.05$) increase in APC (Table 1; Fig. 1a) by 47.8%. Addition of propranolol to the perfusion solution after addition of blood serum from a psoriasis patient before hemoperfusion to it had no effect (Fig. 2b), whereas addition of propranolol by the perfusion medium with blood serum from a psoriasis patient after hemoperfusion caused an increase in APC (Fig. 2c). Thus blood serum from psoriasis patients before hemoperfusion caused an increase in APC of the portal vain myocytes similar to the increase in APC induced by the action of the known β-blocker, propranolol. Blood serum form a healthy donor and psoriasis patient after hemoperfusion caused no such increase in APC.

The contractility of myocytes of blood vessels is known to be largely determined by the state of the β-adrenoreceptors [2]; blockade of these receptors by propranolol leads to an increase in APC [20]. This was confirmed by the results of the present investigation. In addition, our investigations showed that the blood serum of psoriasis patients contains low-molecular-weight components capable of interacting actively with β-adrenoreceptors and blocking them. This conclusion is also confirmed, on the one hand, by absence of summation of the effects of the blood serum ultrafiltrate before hemoperfusion and of propranolol, which may be connected with absence of free β-receptors on the membrane surface as a result of their complete interaction with active components of the blood serum before hemoperfusion, and on the other hand, manifestation of the effect of propranolol after its addition to the perfusion solution containing blood serum ultrafiltrate after hemoperfusion, which is probably due to a fall in the blood serum concentration of these active components as a result of hemoperfusion. These results are in agreement with those obtained by other investigators [10, 19].

The mechanism of epidermocyte proliferation is controlled by the intracellular cyclic nucleotide ratio [13, 23]. For instance, lowering the intracellular cAMP concentration leads to stimulation of proliferation. This effect may also be brought about by increased phosphodiesterase activity [12]. In turn, phosphodiesterase activity is stimulated, in particular, by an increase in the concentration of cytoplasmic active Ca [24]. The formation of APC by smooth-muscle cells is known to be determined by the transmembrane flow of Ca ions [1, 11]. The increase in APC during β-receptor blockade by propranolol or by active blood serum components from patients with psoriasis in the present experiments is probably also connected with stimulation of the calcium current.

There is evidence [3, 5-7, 17] of an increase in the intracellular Ca concentration in the pathological foci in psoriasis. This suggests that the stimulation of epidermocyte proliferation observed in psoriasis is connected with abolition of the biological effect of

epidermal chalones, not only on account of competition between active blood serum components of the patients for the epidermocyte membrane receptor, but also on account of stimulation of phosphodiesterase by intracellular Ca. The therapeutic effect of hemoperfusion may be connected with a fall in the concentration of active components in the blood serum capable of affecting processes of tissue-specific regulation of epidermocyte proliferation. As a result of the investigation, active components capable of blocking β-adrenergic receptors of cell membranes were found in the blood serum of psoriasis patients.

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