THE SIGNIFICANCE OF STRESS HORMONES IN PSORIASIS

F. Z. Zangeneh^{1*} and A. Fazeli²

1) Vali-e-Asr Reproductive Health Research Center, Tehran University of Medical Sciences, Tehran-Iran

2) Pharmacology Department, Medical Faculty of Ahwaz University of Medical Sciences, Ahwaz, Iran

Abstract- Psoriasis is a chronic, non-contagious skin condition characterized by inflamed and scaly lesions of skin. Whilst the pathogenesis of psoriasis is not known, psychological stress has been implicated as a potential trigger in the onset and exacerbation of the condition. Psychiatric and psychological factors play an important role in at least 30% of dermatologic disorder and pathophysiologic link between psychological stress (PS) and disease expression remains unclear. Recent studies demonstrated PS-induced alterations in permeability barrier homeostasis, mediated by increased endogenous glucocorticoids. As activation of the hypothalamic pituitary adrenal axis (HPA) is critical to a successful stress response, we investigated this in patients with psoriasis. This study was performed on 55 patients (40 females and 15 males) visited our clinic for treatment of psoriasis in pharmacology department. We measured the rate of activation of HPA by hormonal changes. These patients displayed higher fasting blood sugar (FBS), epinephrine (Ep), adrenocorticotropin hormone (ACTH), aldosterone, prolactin, growth hormone and estradiol hormones value but diminished cortisol and corticotropin releasing factor (CRF). These results show that HPA and psychoneuroendocrine hormones have a significant role in psoriasis.

© 2008 Tehran University of Medical Sciences. All rights reserved.

Acta Medica Iranica 2008; 46(6): 485-488.

Key words: Psoriasis, stress, glucocorticoids, hypothalamic-pituitary-adrenal axis

INTRODUCTION

Today stress is a normal part of every day living. Stress of both physiological and emotional origin has effect on the hypothalamus-pituitary-adrenal (HPA) axis. The best marker in endocrine-stress axis is adrenocorticotropin hormone (ACTH), which reaches to maximum level in the first hour, while cortisol is highest during the second hour of stress (1). In 1995, Saffran and Schally reported that extracts of median eminence contain a substance that stimulates the release of ACTH and they named this substance corticotrophin-releasing factor (CRF). The

Received: 28 Aug. 2006, Revised: 26 Jul. 2007, Accepted: 21 Sept. 2007

* Corresponding Author:

Farideh Zangeneh, Department of Pharmacology, School of Medicine, Ahwaz University of Medical Sciences, Ahwaz, Iran Tel: +98 912 23752767 Fax: +98 2166581658 E-mail: zangeneh14@gmail.com CRF as a major regulator of HPA axis was first isolated due to its ability to stimulate the release ACTH; later it was also found to have a wide spectrum of actions within the central nervous system (2).

The stress system orchestrates body and brain responses to the environment. This action exerted by the mediators of the stress system has two modes of operation. The stress neuropeptides, CRF and its structurally related peptide urocortin, modulate the inflammatory response via the hypothalamuspituitary-adrenal axis and locally, in a paracrine manner, act on mast and macrophage cells. The immediate response mode driven by CRF via CRF-1 receptors organizes the behavioral, sympathetic and hypothalamic-pituitary-adrenal (HPA) responses to a stressor. In the other slower mode, which facilitates behavioral adaptation, the urocortins acting through CRF-2 receptors seems to be prominent (3).

Corticosteroid hormones secreted by the adrenal cortex are implicated in both modes through their high affinity type 1 (mineralocorticoid receptors-MR) and lower affinity type 2 (glucocorticoid receptors - GR) receptors that are co-localized in limbic neural circuitry. Present data propose that MR controls the threshold or sensitivity of the fast CRF-1 driven stress system mode and thus prevents disturbance of homeostasis, while GR facilitates its recovery by restraining in these very same circuits stress responses by mobilizing energy resources. In preparation for future events, GR facilitates behavioral adaptation and promotes storage of energy. The balance in the two stress system modes is thought to be essential for cell homeostasis, mental performance and health.

Imbalance induced by genetic modification or chronic stressors changes specific neural signaling pathways underlying psychic domains of cognition and emotion, anxiety and aggression. The highest density of CRF-containing cell bodies is found in the medial parvocellular division of the hypothalamic paraventricular nucleus (PVN) with the majority of cells projecting to the median eminence. This CRF pathway comprises the hypothalamic component of the endocrine stress axis (4).

CRF, urocortin and their receptors are also present in the skin and their levels are increased following stress. Human mast cells synthesize and secrete both CRF and urocortin in response to immunoglobulin E receptor (Fc epsilon RI) cross linking. Mast cells also express CRF receptors, activation of which leads to the selective release of cytokines and other pro-inflammatory mediators (5).

Mast cells are involved in atopic disorders, often exacerbated by stress, and are located perivascularly close to sympathetic and sensory nerve endings. Mast cells are activated by electrical nerve stimulation and millimolar concentrations of neuropeptides, such as substance P. Moreover, acute psychological stress induces CRF-dependent mast cell degranulation. Intradermal administration of rat/human CRF (0.1-10 microM) in the rat induced mast cell degranulation and increased capillary permeability in a dose-dependent fashion. Recent evidence suggests that crosstalk between mast cells, neurons and keratinocytes might be involved in such exacerbation. Mast cells are distributed widely in the skin, are present in increased numbers in atopic dermatitis and are located in close proximity to substance P or neurotensin-containing neurons (6).

Activation of the HPA axis is critical to a successful stress response in patients with psoriasis and in particular those whose disease appears to be stress responsive, exhibit an altered HPA response to acute social stress (7). Recent studies demonstrated psoriasis induced alterations in permeability barrier homeostasis, mediated by increased endogenous glucocorticoids (8). The stresses caused by psoriasis have been divided into two groups. In the first, stress is caused by anticipating other peoples' possible reactions, and this can lead to the avoidance of worrying situations such as going to public places. Secondly, stress can arise from patients' beliefs about, or the actual experience of, being evaluated by others on the basis of the skin condition, for example dealing with people who seem to avoid contact with the lesions of psoriasis (9). A large proportion of people with psoriasis believe that stress is a causal factor in their illness and they sure that stress triggered their psoriasis originally (10, 11), and this belief was associated with poorer psychological well-being and the perception that psoriasis has a large emotional impact (12, 13).

In this study, we investigated hypothalamuspituitary-adrenal axis in patients with psoriasis.

MATERIALS AND METHODS

After diagnosis of psoriasis provided by a dermatologist, individuals with chronic plaque psoriasis were recruited, and they visited in clinic of pharmacology department for treatment. Ethics committee of our institution approved the study protocol and we obtained informed consent from all participants.

Fifty five patients (40 females and 15 males) were selected and function of HPA axis was evaluated by demonstrating response to dexamethasone (1 mg) suppression test and measurement of the serum level of these hormones: cortisol, CRF, epinephrine, growth hormone, aldosterone, prolactin, ACTH, estradiol and fasting blood sugar (FBS) by kit and ELISA method.

Differences in mean serum hormones and FBS between psoriasis patients and normal were compared by Student Paired *t* test. All values are given as the mean \pm SEM.

RESULTS

In this study 55 patients (72% were female and 28% were male), with mean age of 31 years were evaluated. Psoriatic patients showed markedly low cortisol values and suppression of CRF, but other hormones (including epinephrine, growth hormone, aldosterone, prolactin, ACTH, estradiol) and FBS were significantly higher than normal. The result of the blood factors measured in this study is demonstrated in the Table 1.

DISCUSSION

Our results (hypocortisolism, low CRF and higher adrenaline values) confirm previous findings that there is a relationship between psoriasis and stress.

It seems that pathogenesis of psoriasis is subject to control by higher neuro-hormonal systems. Measurement of free plasma catecholamines by a standardized HPLC method in patients with psoriasis show that the concentrations of circulating adrenaline and noradrenaline are significantly higher than control groups (14), that means down regulation of catecholamines receptors. Also the effect of epinephrine on the cyclic AMP level measured by microdissection technique has been showed that psoriatic involved epidermis for each had a reduction

Hormones	Normal	Psoriasis patients
Cortisol	280 ± 20	194 ± 10.2
CRF	217 ± 61	145.1 ± 8
Adrenaline	94 ± 12	125 ± 2.45
Ald	85 ± 36	152 ± 6.01
GH	< 7	14.2 ± 0.86
FBS	90 to 110	203 ± 13.3
PRL	2 to 18	29.2 ± 1.6
ACTH	2.2 ± 13.2	25.11 ± 1.83
Estradiol	3.67	10.55 ± 0.75

Abbreviations: CRF, corticotrophin-releasing factor; GH, growth hormone; FBS, fasting blood sugar; PRL, prolactin; ACTH, adrenocorticotropin hormone.

of beta-adrenergic responsiveness (down regulation of receptors), which might be significantly involved in the pathophysiology of psoriasis (15).

Histological examination of the skin shows that the epidermis significantly thickens and the number of mast cells in the dermis significantly increases by repeated exposure to stress, and these changes can be blocked by a selective CRFR type 1 (CRFR1) antagonist (CRA1000). CRFR1 is involved in the stress-induced exacerbation of chronic contact dermatitis and immunoreactive CRF receptor type 1 (CRH-R1) was expressed abundantly on vascular endothelial cells and discrete perivascular cell populations, identified as mast cells (16-23). Reverse transcriptase-polymerase chain reaction analysis was performed to examine CRF receptor subtype messenger RNA (mRNA) expression in RA, PsA, and normal synovial tissue. In addition, CRF receptor expression was examined in isolated synovial endothelial cells and synoviocytes. Selective up-regulation of CRF receptors in inflamed synovial tissue indicated that CRF functions locally, in an autocrine/paracrine receptor-mediated manner (16).

Cortisol may be involved in the clinical eruption phase and epinephrine in the remission phase and produced in excess via the pituitary-adrenal axis (18, 19). The plasma levels of human growth hormone, prolactin (20, 21), ACTH, aldosterone and prolactin in psoriatic patients were higher than normal (22), these findings confirm our study. The level of serum estradiol (23) and FBS in psoriatic patients were higher than normal, which indicates to delay of healing process plaque of psoriasis.

This study shows that patients with psoriasis, and in particular those whose disease appears to be stress responsive, exhibit an altered HPA response to stress and HPA response play a major and critical role in pathogenesis of psoriasis.

Conflict of interests

The authors declare that they have no competing interests.

REFERENCES

1. Dobson H, Smith RF. What is stress, and how does it affect reproduction? Anim Reprod Sci. 2000 Jul 2;60-61:743-752.

- 2. Rivier C, Rivest S. Effect of stress on the activity of the hypothalamic-pituitary-gonadal axis: peripheral and central mechanisms. Biol Reprod. 1991 Oct; 45(4):523-532.
- Charalampopoulos I, Androulidaki A, Minas V, Chatzaki E, Tsatsanis C, Notas G, Xidakis C, Kolios G, Kouroumalis E, Margioris AN, Gravanis A. Neuropeptide urocortin and its receptors are expressed in rat Kupffer cells. Neuroendocrinology. 2006; 84(1): 49-57.
- 4. de Kloet ER. Hormones, brain and stress. Endocr Regul. 2003 Jun; 37(2):51-68.
- Theoharides TC, Donelan JM, Papadopoulou N, Cao J, Kempuraj D, Conti P. Mast cells as targets of corticotropin-releasing factor and related peptides. Trends Pharmacol Sci. 2004 Nov;25(11):563-568.
- Theoharides TC, Singh LK, Boucher W, Pang X, Letourneau R, Webster E, Chrousos G. Corticotropinreleasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. Endocrinology. 1998 Jan;139(1):403-413.
- Richards HL, Ray DW, Kirby B, Mason D, Plant D, Main CJ, Fortune DG, Griffiths CE. Response of the hypothalamic-pituitary-adrenal axis to psychological stress in patients with psoriasis. Br J Dermatol. 2005 Dec;153(6):1114-1120.
- Choi EH, Brown BE, Crumrine D, Chang S, Man MQ, Elias PM, Feingold KR. Mechanisms by which psychologic stress alters cutaneous permeability barrier homeostasis and stratum corneum integrity. J Invest Dermatol. 2005 Mar; 124(3): 587-595.
- Fortune DG, Main CJ, O'Sullivan TM, Griffiths CE. Quality of life in patients with psoriasis: the contribution of clinical variables and psoriasis-specific stress. Br J Dermatol. 1997 Nov;137(5):755-760.
- 10. Jobling RG. Psoriasis -- a preliminary questionnaire study of sufferers' subjective experience. Clin Exp Dermatol. 1976 Sep; 1(3): 233-236.
- Gupta MA, Gupta AK, Watteel GN. Early onset (< 40 years age) psoriasis is comorbid with greater psychopathology than late onset psoriasis: a study of 137 patients. Acta Derm Venereol. 1996 Nov; 76(6): 464-466.

- O'Leary CJ, Creamer D, Higgins E, Weinman J. Perceived stress, stress attributions and psychological distress in psoriasis. J Psychosom Res. 2004 Nov; 57(5):465-471.
- Gupta MA, Gupta AK. Age and gender differences in the impact of psoriasis on quality of life. Int J Dermatol. 1995 Oct;34(10):700-703.
- 14. Ionescu G, Kiehl R. Increased plasma norepinephrine in psoriasis. Acta Derm Venereol. 1991;71(2):169-170.
- Iizuka H, Umeda K, Koizumi H, Aoyagi T, Miura Y. Epinephrine-induced cyclic AMP accumulation in the psoriatic epidermis. Acta Derm Venereol. 1981; 61(5): 391-395.
- 16. McEvoy AN, Bresnihan B, FitzGerald O, Murphy EP. Corticotropin-releasing hormone signaling in synovial tissue from patients with early inflammatory arthritis is mediated by the type 1 alpha corticotropin-releasing hormone receptor. Arthritis Rheum. 2001 Aug; 44(8):1761-1767.
- 17. Cao J, Papadopoulou N, Kempuraj D, Boucher WS, Sugimoto K, Cetrulo CL, Theoharides TC. Human mast cells express corticotropin-releasing hormone (CRH) receptors and CRH leads to selective secretion of vascular endothelial growth factor. J Immunol. 2005 Jun 15;174(12):7665-7675.
- Weigl BA. The significance of stress hormones (glucocorticoids, catecholamines) for eruptions and spontaneous remission phases in psoriasis. Int J Dermatol. 2000 Sep;39(9):678-688.
- Augey F, Dissard C, Normand I, Daumont M. Generalized pustular psoriasis (von Zumbusch) following iatrogenic hypocortisolism. Eur J Dermatol. 2004 Nov-Dec;14(6):415-417.
- 20. Giasuddin AS, El-Sherif AI, El-Ojali SI. Prolactin: does it have a role in the pathogenesis of psoriasis? Dermatology. 1998;197(2):119-122.
- 21. Paus R. Does prolactin play a role in skin biology and pathology? Med Hypotheses. 1991 Sep;36(1):33-42.
- Valentino A, Fimiani M, Bilenchi R, Castelli A, Francini G, Gonnelli S, Gennari C, Andreassi L. [Therapy with bromocriptine and behavior of various hormones in psoriasis patients]. Boll Soc Ital Biol Sper. 1984 Oct 30;60(10):1841-1844. Italian.
- Murase JE, Chan KK, Garite TJ, Cooper DM, Weinstein GD. Hormonal effect on psoriasis in pregnancy and post partum. Arch Dermatol. 2005 May;141(5):601-606.