PSYCHONEUROIMMUNOLOGIC ASPECTS OF SKIN DISEASES

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SUMMARY – As mental and psychological issues are important in the development of many dermatologic diseases, these factors are of special interest in research. Psychoneuroimmunology is the study of interaction between psychological processes and the nervous and immune systems of the human body, and it was comprehensively described for the first time about 30 years ago. Communication between the mind and the skin involves the psycho-immuno-endocrine-cutaneous system, encompassing the activities of the brain, the immune system and the skin, with participation of different neuropeptides, interleukins, and immune system messengers. Many common dermatologic diseases have some form of psychomediated pathogenesis that partially accounts for the development of skin lesions. There is a link between emotional stressors (acute or chronic), psychiatric diseases, and dermatoses (e.g., psoriasis, atopic dermatitis, urticaria, viral warts, herpes simplex, vitiligo, acnes, alopecia, prurigo, etc.) and different cytokines and mediators produced in the skin and involved in their pathogenesis. A prominent role is played by those agents that belong to the hypothalamic-pituitary-adrenal axis.

Key words: *Psychoneuroimmunology; Skin; Skin diseases; Interleukins; Neuropeptides; Hormones*

Introduction

Mental and psychological issues are important in the genesis and development of many diseases, including different dermatoses[1]. Psychoneuroimmunology encompasses the interaction of the nervous system and immunity, being for the first time comprehensively described about 30 years ago, although the influence of mental status on the course and outcome of numerous diseases had been suspected long before[1-4]. The primary route of communication between the mind and the body is the psycho-immuno-endocrine-cutaneous system, connecting the activity of the brain, the immune system, and the skin. This communication involves different neuropeptides, interleukins, immune system messengers, hormones, etc. There is clinical and experimental evidence that the brain can start, affect, and halt biological skin events and that the skin, as a relevant part of the 'diffuse brain', can modify the quality of perceptions and feelings.

Many common dermatologic diseases have some form of psychomediated pathogenesis that partially accounts for the development of lesions. Clinical observations support a link between emotional stressors (acute or chronic), psychiatric diseases, and many dermatoses and also report positive effects of psychopharmacology and psychotherapy in their treatment. Thus, different dermatoses can be associated with some psychomediated mechanism, e.g., psoriasis, atopic dermatitis (AD), urticaria, viral warts, herpes

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simplex, vitiligo, acnes, hyperhidrosis, effluvium, alopecia, idiopathic itch, lichen simplex, rosacea, seborrheic dermatitis, etc.[1].

The main neuroendocrine and nervous pathways of carrying out the physiological effect of psychological, biological, and social factors on the immunity and disease development are the hypothalamic-pituitary-adrenal axis (HPA axis) and the sympathetic, adrenomedullary, and parasympathetic systems[2]. These systems react to stressogenic stimuli and can cause pathological occurrences in acute or chronic stress. It is significant that stress resistance can be enhanced by personal coping mechanisms, social support, and favorable psychosocial constellations.

According to the biopsychosocial model, psychosocial factors interact with the person's biological characteristics (e.g., genetic or constitutional) engendering vulnerability to disease processes[5]. Thus, genetic predisposition to disease development ('diathesis') may remain latent until stress events, represented as an interaction between the biopsychosocial factors and the person's biology[2]. Psychological and social factors are believed to influence disease processes *via* two main mechanisms: psychosocial processes (e.g., mental health and mood factors, personality characteristics, resources, social relationships) and health-oriented behaviors (e.g., hygiene, protective measures such as sun protection, exercise, nutrition, smoking)[2,6].

Studies have shown the association between illness, behavior and psychological state (anxiety, depression, sleep loss, bereavement, etc.) and certain external stress factors (e.g., family illness, academic stress, unemployment), which seem to affect the immune system in some way[4,7]. As data on personality and coping suggest, differences in perceptions and reactions to the same events can provoke different endocrine and immune responses. In fact, neuroendocrine mechanisms may mediate the associations between personality and coping styles and immune function[2,8].

When talking about the skin, the neuroendocrine substances originate from nerve fibers that innervate it, or from skin cells that can produce and secrete humoral signal molecules (neurotransmitters, neuropeptides and hormones), which enter the HPA axis and are analogous to its own neurotransmitters, neuropeptides and hormones[2]. Neuromediators in the skin also include classical neurotransmitters (catecholamines and acetylcholine), released from autonomous nerve fiber endings in the skin and skin cells. Skin proteinases also have a regulatory role in immune and inflammatory reactions, acting as enzymes or ligands of specific receptors (proteinase-activated receptor, PAR).

It is important that there is also evidence that at the local level (in the skin) a neuroendocrine control mechanism exists, similar to the central one that acts at the level of the whole body.

Cellular Elements of the Skin Immune System and Cytokine Secretion

In the epidermis and dermis, there are various immune cells [keratinocytes, dermal dendritic cells (DCs), epidermal Langerhans cells (LSs), melanocytes, T cells and others], which reach the skin through recirculation[2]. So, when stimulated, skin cells (primarily keratinocytes) produce various cytokines. Although keratinocytes of healthy skin do not express class II major histocompatibility complex (MHC-IL) or adhesion molecules ICAM-l (an important component for antigen presentation), it is possible in some skin diseases (acting as accessory cells that stimulate proliferation of antigen-stimulated T cells)[2].

Keratinocytes synthesize various chemokines and cytokines that act through corresponding receptors on skin cells, having numerous effects on the migration of inflammatory cells, proliferation and differentiation of keratinocytes, synthesis of other cytokines, and on the immune system. After skin contact with the antigen, keratinocytes are activated and produce and secrete various cytokines and chemokines, through which they regulate inflammatory and immune reactions in the skin. Activated keratinocytes secrete proinflammatory cytokines (IL-1α, IL-6, IFN-γ), which enhance migratory activity of LCs leaving for regional lymph nodes, where they stimulate proliferation of specific T cells[9]. Thus, keratinocytes can have a role of accessory cells for antigen presentation (under the influence of proinflammatory cytokine IFN-γ they express MHC-lI). Specific T cells enter the circulation and, attracted by chemokines, arrive in the skin where they remain due to increased expression of adhesion molecules on endothelial cells of dermal blood vessels. After initial stimulation of inflammatory and immune reactions, they are inhibited to preserve ho-

meostasis [keratinocytes participate by secreting antiinflammatory cytokines IL-10 and transforming growth factor-β (TGF-β)][2,9].

Keratinocytes produce IL-1 and IL-6 whose basal synthesis is enhanced by some allergens or superantigens. IL-1 is stored in the skin (predominantly as IL-1α) and probably waits to act immediately after an injury or bionoxa. So, IL-1α induces several genes in skin cells, including keratinocytes, fibroblasts (FBLs) and endothelial cells of blood vessels, e.g., genes for adhesion molecules, chemokines, cytokines, proteolytic enzymes and matrix proteins. Keratinocytes also produce IL-6, which stimulates keratinocyte proliferation and it is important in different pathologic conditions (e.g., psoriasis, lichen planus, wound healing), after exposure to UV radiation or after treatment with tumor necrosis factor (TNF-α)[2].

Keratinocytes also produce immunomodulatory cytokines that have systemic effects, IL-10 and IL-12, and act antagonistically. After exposure to UV radiation, immunosuppression occurs for which keratinocyte IL-10 is responsible because it shifts the cytokine profile from T helper type 1 (Th1) to T helper type 2 (Th2) cell type (suppresses cellular immunoreaction). On the other hand, IL-12 has an important role in Th1 response induction. It was found that allergens stimulate keratinocytes to secrete IL-12, as in allergic contact dermatitis (as opposed to irritant contact dermatitis). Recently, it has been shown that keratinocytes secrete IL-18, a key mediator that induces Th1 response (e.g., in AD).

It is significant that keratinocytes synthesize growth factor and chemokines (IL-8, TNF-α). Chemokines are small cytokines which, during inflammation, are involved in chemotaxis, cell migration and activation, especially of phagocytes and lymphocytes. Thereby, IL-8 is a chemotactic factor for neutrophils and is secreted after contact with various irritants and in autoimmune skin diseases, while TNF-α is released after UV radiation (when it induces keratinocyte apoptosis) and in some skin diseases (e.g., psoriasis and skin T-lymphomas)[2].

The Role of Hypothalamic, Hypophyseal and Adrenocortical Hormones

It has been determined that skin produces hypothalamic and hypophyseal signal peptides, which are secreted in the intercellular space. So, epidermal keratinocytes and dermal FBLs synthesize hypothalamic and hypophyseal signal peptides and express receptors for them[2]. Thus, the skin synthesizes all peptide hormones that enter the HPA axis (the main mediator in stress response), hypothalamic corticotropin-releasing hormone (CRH) and urocortin (a peptide similar to CRH). CRH is a central component of the HPA axis and regulates the expression of pro-opiomelanocortin (POMC) and pituitary POMC-derived peptides [(ACTH, α-melanocyte-stimulating hormone (α-MSH) and β-endorphin)] (from the anterior pituitary gland)[10].

The skin is directly exposed to various environmental stressors (UV radiation, pathogens, thermal and chemical insults) and the skin cells have developed a number of defense mechanisms that are coordinated by messages from the local neuroendocrine-immune system. The predominant skin stressor from the environment is sun radiation (particularly the UV spectrum) that increases the expression of the gene for prostaglandin metabolism and the genes for IL-1, IL-6, IL-8, IL-10, for some metalloproteinases, whilst decreasing the activity of the genes for growth factors (KGF, FGF). It has been found that UV radiation leads to increased expression of CRH receptor (CRH-R1).

Recent studies have identified the existence of a peripheral skin stress response system (equivalent to the central HPA axis)[11-13]. It is well known that pituitary ACTH stimulates adrenal cortisol and glucocorticoid production. Stress influences cellular and humoral immune responses by releasing glucocorticoid, catecholamine, and CRH and POMC peptide secretion as well as by altering cytokine profiles[11,12]. Accordingly, the skin would be a peripheral neuroendocrine organ, and local homeostasis is regulated through hormones, neurotransmitters, neuropeptides, cytokines and their receptors[11-15]. Also, the presence of CRH, urocortin, POMC-derived peptides and their receptors is proven in normal skin: in the epidermis, hair follicles, blood vessel walls, etc. Thus, HPA axis activation at the central, hypothalamic level is stimulated by hormones in the skin, which are a product of various cellular elements[2].

POMC is a significant hypophyseal hormone (also found in the skin and other organs), a precur-

sor molecule by whose breakdown [by serine proteases PC1 and PC2 (prohormone-convertase)] active neuropeptides and neurohormones are created: MSH (α-MSH, β-MSH, γ-MSH), ACTH, β-lipotropic hormone (β-LPH)) and β-endorphin. These peptides are bound to melanocortin receptors on skin cells: MC-1R (binds α-MSH and ACTH) and MC-2R (selectively binds ACTH). Thus, POMC and its dissolution peptides participate in growth regulation and differentiation, immunomodulatory activities and melanogenesis stimulation, and is found in the skin in keratinocytes, melanocytes, DCs and FBLs. The level of POMC peptide is low in healthy skin and increased in various skin diseases (e.g., AD, melanoma, carcinoma). The expression of POMC is increased under the influence of proinflammatory cytokines (IL-l, IL-6, TNF-α) and UV radiation, and decreased under the influence of antiinflammatory cytokine TGF-β[2].

α-MSH is a neuropeptide (13-amino-acid polypeptide) derived from POMC and primarily a hypophyseal product (but also synthesized in the skin), whose immune-modulating activity seems to inhibit skin inflammation. Thus, α-MSH modulates inflammatory and immune response (by anti-inflammatory action), and it increases the secretion of anti-inflammatory cytokines (IL-10), suppresses the secretion of proinflammatory cytokines (IL-l, IL-6, TNF-α) and limits antigen presentation (decreases expression of MHC-1 and co-stimulatory molecules on DCs).

The skin can also release α-MSH during the process of synthesis and release of POMC, its derivatives and a series of other substances [substance P (SP), calcitonin gene-related peptide, vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), etc.][1]. Skin cells and Aδ and C nerve fibers release neuropeptides that link the nervous system and the skin itself. Furthermore, α-MSH may regulate the expression of cell mediators on the surface of immune cells and decrease IFN-γ release from activated lymphocytes. α-MSH also seems to interfere with leukocyte migration from blood to the sites of inflammation, modifying the expression of leukocyte and endothelial adhesion molecules and endothelial leukocyte and vascular cell adhesion molecules-1 (VCAM-1). Thus, α-MSH and other neuropeptides may function as a potential therapeutic, anti-inflammatory agent in dermatology.

The Role of Corticotropin-Releasing Hormone

Stress activates several neural pathways, but the main stress response systems are the locus caeruleus, sympathetic-adrenal-medullary system, and HPA axis[12-16]. The stressors stimulate the paraventricular nuclei of the hypothalamus, whereas the corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) are synthesized. Thus, CRH stimulates the secretion of AVP (which has a synergistic effect with CRH), particularly under chronic stress, while pituitary ACTH stimulates adrenal cortisol and glucocorticoid production.

It can be said that the skin is homologous to the HPA axis and corresponds in organization to the central hypothalamic-hypophyseal axis, CRH-POMC-ACT[13,14]. Recently, it has been demonstrated that dermal FBLs respond to CRH by activating the gene for POMC, and subsequently by secreting ACTH[2]. Thus, FBLs demonstrate a functional CRH-POMC-ACTH-corticosterone axis similar to the hypothalamus-hypophysis-adrenal gland axis (systemic response to stress), except that FBLs synthesize corticosterone (instead of cortisol). In contrast to FBLs, keratinocytes do not respond to ACTH by secreting corticosterone, although they express CRH–R1 and the gene for POMC (they do not demonstrate a functional CRH-POMC axis).

Normal skin expresses CRH, urocortin, POMC-derived peptides and their receptors. Various skin cells can secrete CRH (including epidermal and hair follicle keratinocytes, sebocytes and mast cells), and melanocytes and FBLs response to local CRH stimulation, confirming the presence of a functional local HPA axis[12-16]. Local production of stress hormones of the HPA axis enables the skin to regulate local homeostasis under stress.

CRH acts through CRH receptor (CRH-R), which belongs to the calcitonin/VIP/growth hormone-releasing hormone subfamily of the G protein-coupled receptors. These include CRH-R1 (the major receptor in the epidermis and dermis) and CRH-R2 (the predominant type of receptor in adnexal structures)[17]. CRH has a different skin effect, i.e. stimulates diverse signaling pathways (*via* CRH-R1 activation), which modulate proliferation, differentiation, apoptosis and pro- or anti-inflammatory activities of skin cells[18].

CRH activates various skin cells to release the proinflammatory cytokines (e.g., IL-6 release by keratinocytes and IL-1β release by monocytes). As skin mast cells function as 'sensors' of environmental and emotional stress, their CRH-induced activation may be associated with exacerbation of skin diseases[12,19]. CRH and urocortin activate skin mast cells (through activation of CRH-R1) and increase mast cell's selective release of vascular endothelial growth factor (VEGF) and IL-6 (vascular permeability)[19]. Moreover, human mast cells can produce CRH and urocortin.

It could also be mentioned that local concentration of neuropeptides and some chemokines is adjusted by peptidases on skin cell membranes. Some peptidases are expressed on mastocytes, e.g., the neutral peptidase (NEP; CD10), which regulates the concentration of several neuropeptides (substance P, VIP and bradykinin), and adjusts the concentration of opioid peptides Len-enkephalins and Met-enkephalins[2].

Hence, CRH has anti-inflammatory activity and diminishes NF-kB activation in epidermal melanocytes and inhibits IL-18 expression [through the mitogen-activated protein kinase (MAPK) signaling pathway] in human HaCaT keratinocytes (cell type belonging to an immortal human keratinocyte line used in scientific research)[20]. ACTH stimulates human keratinocytes to secrete IL-18 through melanocortin receptors (MC1R and MC2R), p38 and ERK MAPK pathways. Since CRH inhibits IL-18 expression in HaCaT cells, IL-18 may play an important role in the negative feedback loop of CRH regulation[21].

The Influence of Psychosocial and Psychiatric Factors on Dermatologic Diseases

Only a few clinical and experimental studies have investigated the association of psychoneuroimmunology and skin diseases (psoriasis, AD, urticaria, viral warts, herpes simplex, vitiligo, acnes, itch, etc.). However, the majority of observations are limited to comparison of clinical pictures of skin diseases and psychological states.

It has been observed that psoriasis is worsened by stress, but there is no clear evidence defining the exact pathomechanisms[1]. Many psoriatic patients believe that there is a causal relationship between stressors and their disease outcome. Earlier studies have suggested that exacerbation of psoriasis occurs a few weeks to months after a stressful event, which might be related to the alteration of the HPA axis and the release of neuropeptides[12,22]. Thus, a recent prospective study demonstrated a positive significant correlation between preceding daily stressors and clinical pictures (Psoriasis Area and Severity Index) and itch (4 weeks later)[23].

Earlier studies found a hyporesponsiveness of HPA axis function in psoriatic patients during exposure to an acute stressor, which might result in exaggerated clinical picture due to diminished suppressive effect of the low level of cortisol (indicating they are more vulnerable to the influence of stressors)[12]. Recent data revealed associations between daily stressors and an increase in disease severity a month later, with a significant association between the highest levels of daily stressors and a lower cortisol level. Schmid-Ott *et al.* proved that after a psychosocial stress, psoriatic patients showed an increased number of activated T cells with a shift towards Th1-cytokines and an increased number of cutaneous lymphocyte-associated antigen-positive T cells and natural killer (NK) cells (relevant in aggravation of psoriatic plaques)[24]. However, other studies demonstrated no alteration of the HPA axis function in psoriasis, indicating that the systemic HPA axis response could be normal in a Th1-dominant inflammatory condition[12,25].

It is interesting to observe the role of β-endorphin (one of the POMC-related peptides) in psoriasis, which is produced by the HPA axis or secreted by immune cells. Psoriatic patients with actively spreading plaque lesions showed increased serum β-endorphin and high lesional β-endorphin, which might induce SP-mediated neurogenic inflammation and has an anti-nociceptive effect on peripheral sensory nerve function (possibly responsible for the absence of itching). It is supposed that β-endorphin may be produced by lesional inflammatory cells rather than by the activation of HPA axis in chronic stress[12].

Many researchers focus on the proinflammatory role of CRH in psoriasis. So, CRH may activate mast cells (*via* CRH-R), leading to the release of histamine with increased vascular permeability. Simultaneously, mast cells secrete the proinflammatory cytokines IL-1, IL-6 and TNF-α (up-regulated in psoriatic skin), which are potent stimulators of CRH and POMC

production in the skin. In psoriasis, increased serum CRH and decreased lesional CRH/CRH-R1 gene expression suggest that down-regulated lesional CRH/CRH-R1 expression in psoriatic lesions may be the result of negative feedback of systemic CRH elevation. Thereby, CRH might have a protective function from developing psoriatic lesions[12].

However, there are also some conflicting results of peripheral HPA axis expression in psoriatic lesions[12,18]. The exposure to stressors (real life and experimental) showed dysregulated HPA activity, which might result in changes of immune responses and peripheral CRH levels. Inflammatory mediators released from psoriatic lesions interact with peripheral HPA axis and may influence the central HPA axis, which should be studied further[12,26].

Concerning AD, a chronic allergic skin disease, psychological aspects of the disease must also be taken into account. Investigations have revealed that in AD patients psychological factors seemed to increase serum IFN-γ and IL-4, whereas NK activity was decreased mainly by anxiety (not by psychosomatic complaints)[1].

The studies also suggest that psychological stress triggers and aggravates AD by involving the activation of the HPA axis and inducing a shift toward Th2 cell phenotype[12]. After stress, AD patients showed blunted HPA axis responsiveness and increased reactivity of the sympathetic adrenomedullary system[27]. Interestingly, neonates with a parental atopic history and elevated cord IgE had significantly increased HPA responsiveness to the stress of heel prick (possibly due to hormonal effect to maternal stress), which may increase the vulnerability to develop AD later in life. Additionally, adolescents with AD had an attenuated cortisol response to laboratory stress. However, Afsar *et al*. identified that AD children did not differ in basal cortisol levels or anxiety compared with normal children[28].

There is also an influence of stress-induced CRH on the immune response and DCs which promote allergic responses by inducing Th2 cell differentiation. So, Lee *et al*. detected CRH-R1α, 1β, 2α mRNA and CRH-R1, CRH-R2 protein in mononuclear cell-derived DCs in AD patients and revealed that CRH significantly decreased the expression of IL-18 in DCs[29,30]. In AD patients, stress-induced CRH may enhance Th2 immune responses by acting directly on DCs (*via* CRH-R) and may aggravate the disease[29,30].

Additionally, patients with severe AD have increased serum levels of β-endorphin produced from lesional inflammatory cells (rather than by activation of central HPA axis in chronic stress). Thereby, stress-related pruritus may be associated with a systemic pruritic effect of β-endorphin[29,31,32]. It has been found that exercise-induced stress differently affects the AD symptoms and POMC-related hormone level, depending on the strength of exercise. As β-endorphin strengthens natural immunity, proper exercise might be helpful to control the AD symptoms by stimulating the HPA axis and inducing balanced Th1/Th2 immunity.

Exacerbation of AD due to stress also manifests through mast cell activation[29]. In the presence of stem cell factor (SCF) and IL-4, mast cells produce mostly Th2-cytokines and release neuropeptides (such as SP and nerve growth factor, NGF)[19]. Experimental stress in AD patients also stimulates enhanced allergen-specific immune responses with elevated levels of plasma SP, VIP and NGF, and concomitant increase of Th2-cytokines[33]. There are few studies about local stress hormone expression in AD lesions. The neuropeptides NGF and NPY are known to be associated with anxiety (anxiety score positively correlated with pruritus in AD patients)[33]. According to study results, the epidermis of AD skin lesions showed significantly higher NGF and NPY expression, indicating that they participate in the activation of intraepidermal mast cells, contributing to stress-induced pruritus[34,35].

AD patients also showed blunted HPA axis responses to stressors. In general, stress negatively affects the severity of AD by down-regulating cellular immunity and enhancing humoral immunity. Thus, CRH and POMC-related peptide hormones, as well as the neuropeptides SP, NGF and NPY modulate immune and inflammatory response under stress. However, psychological interventions have been shown to have positive effects on skin status, itch and scratching behavior in patients[36].

Regarding urticaria, it has also been indicated that psychological factors may contribute to its occurrence, especially in chronic urticaria. Psychosocial and psychiatric factors may act in the pathogenesis of urti-

caria, mostly by increasing the release of neuro- and immune mediators, mainly from mast cells (e.g., IL-4, IL-5, IFN-γ, and TNF-α) and the release of vasoactive peptides (including histamine)[1].

There is also evidence of the psychoneuroimmune mechanisms in the pathogenesis of vitiligo[37]. Some investigators revealed a higher number of stressful life events in these patients compared to controls, as well as abnormal secretion of neuromediators (e.g., β-endorphin and metenkephalin) and higher immunoreactivity to NPY and VIP. Not all effects of neuropeptides on melanocytes are known, although nervous system seems to play a role in activating melanocytes[1]. Alternatively, clinical and experimental evidence suggests a role of humoral and cellular autoimmunity in vitiligo pathogenesis.

It is important to mention that some infective skin diseases are also under psychological influence (e.g., viral warts, herpes simplex)[38,39].

There are also other dermatologic diseases for which there is evidence of psychological and psychiatric etiological factors. This indicates its importance in considering the possibility that those patients could benefit from cognitive behavioral and psychological therapy[1,40].

As dermatologists and dermatologic patients have long acknowledged the effect of stress on the skin and its capability to initiate, maintain, or exacerbate several skin diseases, it is important to understand skin vulnerability to psychological stress[40-42]. It is significant that stress resistance can be enhanced by personal coping mechanisms, social support, and favorable psychosocial constellations. A multidisciplinary approach for treatment from both dermatologic and psychiatric viewpoints is suggested.

Conclusion

The link between emotional stressors (acute or chronic), psychiatric diseases, and dermatoses (e.g., psoriasis, AD, urticaria, viral warts, herpes simplex, vitiligo, acnes, alopecia, prurigo, etc.) has been evidenced. Thereby, different cytokines, mediators and hormones are produced in the skin and involved in the pathogenesis of these skin disorders. A prominent role is played by those agents that belong to the HPA axis and there is plenty of evidence that the skin includes a neuroendocrine control mechanism similar to the central one. This indicates its importance in considering the possibility that these patients could benefit from cognitive behavioral and psychological therapy or other therapeutic methods. However, the psychological and psychiatric genesis of a skin disease is still a topic of investigation.

References

1. URPE M, BUGGIANI G, LOTTI T. Stress and psychoneuroimmunologic factors in dermatology. Dermatol Clin 2005;23(4):609-17.
2. GABRILOVAC J. Neuroendokrina regulacija imunosnog odgovara u koži. In: BORANIĆ M *et al.*, editors. Psihoneuroimunologija. Zagreb: Školska knjiga, 2008:103-15. (in Croatian)
3. LUGOVIĆ L, ŠITUM M, VURNEK M, BULJAN M. Influence of psychoneuroimmunologic factors on patients with malignant skin diseases. Acta Med Croatica 2007;61(4):383-9.
4. VIDRIH B, KARLOVIĆ D, BOŠNJAK PAŠIĆ M, UREMOVIĆ M, KOVAK MUFIĆ A, MATOŠIĆ A. A review of the psychoneuroimmunologic concepts on the etiology of depressive disorders. Acta Clin Croat 2012;51(3):403-9.
5. ENGEL GF. The need for a new medical model: a challenge for biomedicine. Science 1977;196:129-36.
6. KIECOLT-GLASER JK, McGUIRE L, ROBLES TF. Emotions, morbidity, and mortality. New perspectives from psychoneuroimmunology. Annu Rev Psychol 2002;53:83-107.
7. MOLDOFSKY H, LUE FA, DAVIDSON JR. Effect of sleep deprivation on human immune function. FASEB J 1989;3(8):1972-7.
8. SEGERSTROM SC. Personality and the immune system: models, methods, and mechanisms. Annu Rev Behav Med 2000;22(3):180-90.
9. BAKULA A, LUGOVIĆ-MIHIĆ L, ŠITUM M, TURČIN J, ŠINKOVIĆ A. Contact allergy in the mouth: diversity of clinical presentations and diagnosis of common allergens relevant to dental practice. Acta Clin Croat 2011;50(4):553-61.
10. CHROUSOS GP. Stressors, stress, and neuroendocrine integration of the adaptive response. Ann N Y Acad Sci 1998;30(851):311-35.
11. ELENKOV IJ, CHROUSOS GP. Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. Trends Endocrinol Metab 1999;10(9):359-68.
12. KIM JE, PARK HJ. Stress hormone and skin disease [homepage on the Internet]. Korea: Department of Dermatology, College of Medicine; 2012 [updated 17 May 2012; cited 30 May 2012]. Available from: http://cdn.intechopen.com/pdfs/22589/InTech-Stress_hormone_and_skin_disease.pdf

13. SLOMINSKI A, WORTSMAN J, LUGER T, PAUS R, SOLOMON S. Corticotropin releasing hormone and proopiomelanocortin involvement in the cutaneous response to stress. Physiol Rev 2000;80(3):979-1020.
14. SLOMINSKI A, ZBYTEK B, PISARCHIK A, SLOMINSKI RM, ZMIJEWSKI MA, WORTSMAN J. CRH functions as a growth factor/cytokine in the skin. J Cell Physiol 2006;206(3):780-91.
15. SLOMINSKI A, WORTSMAN J, TUCKEY RC, PAUS R. Differential expression of HPA axis homolog in the skin. Mol Cell Endocrinol 2007;265-266:143-9.
16. ZHANG X, SLIWOWSKA JH, WEINBERG J. Prenatal alcohol exposure and fetal programming: effects on neuroendocrine and immune function. Exp Biol Med (Maywood) 2005;230(6):376-88.
17. PISARCHIK A, SLOMINSKI A. Molecular and functional characterization of novel CRHR1 isoforms from the skin. Eur J Biochem 2004;271(13):2821-30.
18. O'KANE M, MURPHY EP, KIRBY B. The role of corticotropin-releasing hormone in immune-mediated cutaneous inflammatory disease. Exp Dermatol 2006;15(3):143-53.
19. THEOHARIDES TC, ALYSANDRATOS KD, ANGELIDOU A, *et al*. Mast cells and inflammation. Biochim Biophys Acta 2012;1822(1):21-33.
20. PARK HJ, KIM HJ, LEE JH, *et al*. Corticotropin-releasing hormone (CRH) downregulates interleukin-18 expression in human HaCaT keratinocytes by activation of p38 mitogen-activated protein kinase (MAPK) pathway. J Invest Dermatol 2005;124(4):751-5.
21. PARK HJ, KIM HJ, LEE JY, *et al*. Adrenocorticotropin hormone stimulates interleukin-18 expression in human HaCaT keratinocytes. J Invest Dermatol 2007;127(5):1210-6.
22. GUPTA MA, GUPTA AK, KIRKBY S, *et al*. Pruritus in psoriasis. A prospective study of some psychiatric and dermatologic correlates. Arch Dermatol 1988;124(7):1052-7.
23. VERHOEVEN EW, KRAAIMAAT FW, JONG EM, *et al*. Effect of daily stressors on psoriasis: a prospective study. J Invest Dermatol 2009;129(8):2075-7.
24. SCHMID-OTT G, JAEGER B, BOEHM T, *et al*. Immunological effects of stress in psoriasis. Br J Dermatol 2009;160(4):782-5.
25. KARANIKAS E, HARSOULIS F, GIOUZEPAS I, GRIVEAS I, CHRISOMALLIS F. Neuroendocrine stimulatory tests of hypothalamus-pituitary-adrenal axis in psoriasis and correlative implications with psychopathological and immune parameters. J Dermatol 2009;36(1):35-44.
26. LEIBOVICI V, CANETTI L, YAHALOMI S, *et al*. Well being, psychopathology and coping strategies in psoriasis compared with atopic dermatitis: a controlled study. J Eur Acad Dermatol Venereol 2010;24(8):897-903.
27. BUSKE-KIRSCHBAUM A, EBRECHT M, HELLHAMMER DH. Blunted HPA axis responsiveness to stress in atopic patients is associated with the acuity and severeness of allergic inflammation. Brain Behav Immun 2010;24(8):1347-53.
28. AFSAR FS, ISLETEN F, SONMEZ N. Children with atopic dermatitis do not have more anxiety or different cortisol levels compared with normal children. J Cutan Med Surg 2010;14(1):13-8.
29. LEE CH., CHUANG HY, SHIH CC, *et al*. Transepidermal water loss, serum IgE and beta-endorphin as important and independent biological markers for development of itch intensity in atopic dermatitis. Br J Dermatol 2006;154(6):1100-7.
30. LEE HJ, KWON YS, PARK CO, *et al*. Corticotropin-releasing factor decreases IL-18 in the monocyte-derived dendritic cell. Exp Dermatol 2009;18(3):199-204.
31. GLINSKI W, BRODECKA H, GLINSKA-FERENZ M, KOWALSKI D. Increased concentration of beta-endorphin in the sera of patients with severe atopic dermatitis. Exp Dermatol 1995;75(1):9-11.
32. KATSAROU-KATSARI A, FILIPPOU A, THEOHARIDES TC. Effect of stress and other psychological factors on the pathophysiology and treatment of dermatoses. Int J Immunopathol Pharmacol 1999;12(1):7-11.
33. KIMATA H. Enhancement of allergic skin wheal responses in patients with atopic eczema/dermatitis syndrome by playing video games or by a frequently ringing mobile phone. Eur J Clin Invest 2003;3(6):513-7.
34. OH SH, BAE BG, PARK CO, *et al*. Association of stress with symptoms of atopic dermatitis. Acta Derm Venereol 2010;90(6):582-8.
35. DOU YC, HAGSTRÖMER L, EMTESTAM L, JOHANSSON O. Increased nerve growth factor and its receptors in atopic dermatitis: an immunohistochemical study. Arch Dermatol Res 2006;298(1):31-7.
36. SCHUT C, WEIK U, TEWS N, GIELER U, DEINZER R, KUPFER J. Psychophysiological effects of stress management in patients with atopic dermatitis: a randomized controlled trial. Acta Derm Venereol 2013;93(1):57-61.
37. SCHWARTZ R, SEPÚLVEDA JE, QUINTANA T. Possible role of psychological and environmental factors in the genesis of childhood vitiligo. Rev Med Chil 2009;137(1):53-62.
38. DHABHAR FS. Psychological stress and immunoprotection *versus* immunopathology in the skin. Clin Dermatol 2013;31(1):18-30.
39. CHIDA Y, MAO X. Does psychosocial stress predict symptomatic herpes simplex virus recurrence? A meta-analytic investigation on prospective studies. Brain Behav Immun 2009;23(7):917-25.
40. CHUNG WL, NG SS, KOH M, PEH LH, LIU TT. A review of patients managed at a combined psychodermatology clinic: a Singapore experience. Singapore Med J 2012;53(12):789-93.

41. ORION E, WOLF R. Psychological stress and epidermal barrier function. Clin Dermatol 2012;30(3):280-5.

42. BASAVARAJ KH, NAVYA MA, RASHMI R. Relevance of psychiatry in dermatology: present concepts. Indian J Psychiatry 2010;52(3):270-5.

Sažetak

PSIHONEUROIMUNOLOŠKI ASPEKTI KOŽNIH BOLESTI

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S obzirom na to da su mentalne i psihološke značajke važne u razvoju mnogih dermatoloških bolesti, ovi čimbenici su od posebnog interesa za istraživanja. Psihoneuroimunologija obuhvaća međudjelovanje psiholoških procesa, živčanog i imunog sustava te ljudskog tijela, a prvi put je jasno opisana prije oko 30 godina. Komunikacija između psihe i kože uključuje psihološki-imuni-endokrini-kožni sustav obuhvaćajući aktivnosti mozga, imunog sustava i kože, uza sudjelovanje različitih neuropeptida, interleukina i posrednika imunog sustava. Mnoge česte dermatološke bolesti imaju neki oblik psihološki uvjetovane patogeneze koja dijelom doprinosi razvoju kožnih promjena. Pritom postoji veza između emocionalnih stresora (akutnih ili kroničnih), psihijatrijskih bolesti i dermatoza (npr. psorijaza, atopijski dermatitis, urtikarija, akne, virusne bradavice, herpes simpleks, vitiligo, alopecia, prurigo itd.) te različitih citokina i medijatora stvorenih u koži koji su uključeni u njihovu patogenezu. Istaknutu ulogu imaju tvari koje pripadaju osi hipotalamus-hipofiza-nadbubrežna žlijezda.

Ključne riječi: *Psihoneuroimunologija; Koža; Kožne bolesti; Interleukini; Neuropeptidi; Hormoni*