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Psoriasis and Stress – Psoriasis Aspect of Psychoneuroendocrinology

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1. Introduction

Nowadays stress is a normal part of everyday living and the physiological and behavioral consequences of exposure to stressful situations have been extensively studied for decades. The neuroendocrine stress response is a necessary mechanism but disrupts homeostatic process and it is subserved by a complex system located in both the central nervous system (CNS) and the periphery. Stressor-induced activation of the hypothalamus–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS) results in a series of neural and endocrine adaptations known as the "stress response" or "stress cascade." The stress cascade is responsible for allowing the body to make the necessary physiological and metabolic changes required to cope with the demands of a homeostatic challenge. In recent years, evidence has suggested that stress responses are not only under control of the CNS but are influenced by peripheral tissue, outside of the classical HPA axis. Corticotrophin-releasing hormone (CRH) is a central component of the HPA axis and is an important coordinator of the systemic stress response with subsequent modulation of the inflammatory response. In peripheral sites, cutaneous CRH and CRH-receptor1 (CRH-R1) is believed to regulate various functions of the skin that are important for local homeostasis. Common inflammatory skin disorders such as atopic dermatitis and psoriasis exhibit decreased barrier function and recent studies suggest that the complex response of epidermal cells to barrier disruption may aggravate, maintain, or even initiate such conditions.

2. Overview of the stress system

2.1 Historical context

The concept of stress is as old as medical history itself, dating back at least to the time of Hippocrates who referred both to the suffering associated with disease (pathos) and to the toil (ponos) — the fight of the body to restore itself to normalcy (Hippocrates, 1923) . In more recent history, both Walter Cannon (Cannon, 1939) and Claude Bernard (Bernard, 1949) described the ability of all organisms to maintain a constancy of their internal milieu or homeostasis. 70 years ago Hans Selye, the pioneer of contemporary stress research, first described the General Adaptation Syndrome (GAS) as a chronological development of the

response to stressors when their action is prolonged (Selye, 1936). Therefore as pointed out for the first time by Hans Selye in Nature in 1936, stress or 'noxious agents' initiate a reaction in the body, which he called the 'general adaptation syndrome' (GAS). Selye distinguished three stages that the body passes when responding to stress in the GAS: 1) the first stage is an 'alarm reaction', in which the body prepares itself for 'fight or flight'; 2) the second stage of adaptation (provided the organism survives the first stage), is one in which a resistance to the stress is built; and 3) finally, if the duration of the stress is sufficiently long, the body enters a stage of exhaustion, a sort of aging, due to 'wear and tear'.

2.2 Stress system & homeostasis

Life exists by maintaining a complex dynamic equilibrium or *homeostasis* that is constantly challenged by intrinsic or extrinsic adverse forces, the *stressors* (Chrousos et al., 1992). Stress has been defined in many ways. To the physicist, the term refers to a force, strain or pressure applied to a system. However, when the stress response is excessive or in appropriate, it disrupts physiological homeostasis and body function and contributes to disease production (Burchfield, 1979). Although the stress response of the body is meant to maintain stability or *homeostasis,* long-term activation of the stress system can have a hazardous or even lethal effect on the body. For example it increases the risk of obesity, heart disease, depression, and a variety of other illnesses (Selye, 1998). According to Hans Sely, mental, psychologic or sociologic and metabolic stressors (Kvetnansky et al., 2009) tall the stable internal environment of the body, that may contribute directly to the production of disease or it can contribute to the development of certain behaviors that increases the risk of disease. The process that counteracts this disruption and maintains homeostasis is termed allostasis. Allostasis activates a wide range of both general and specific physiological systems and behavioral coping mechanisms. The amount of work carried out during allostasis is termed the allostatic load and represents the cost(s) to the animal of responding to the stimulus. Over the past decade, these terms have been introduced to human stress research to differentiate between adaptation, allostasis and the end result, homeostasis, with the aim of producing a measurement of allostatic load that can be used to compare the effects of a wide range of stimuli. Beyond the "flight-or-fight" response to acute stress, there are events in daily life that produce a type of chronic stress and lead over time to wear and tear on the body ("allostatic load"). Yet, hormones associated with stress protect the body in the short-run and promote adaptation ("allostasis").

2.3 Stress system: Response & adaptation

2.3.1 Transient adaptation: Allostasis

Physiologic systems operate within a dynamic range of steady states and maintain internal balance, or homeostasis, in terms of blood pH and electrolyte concentration. When physical or psychologic stressors challenge the body, there is activation of sympathoadrenal and adrenocortical responses that promote adaptation and survival in the short term. This has been referred to as **allostasis**. For example, during exercise or emotional responses, there is transient activation of the hypothalamic-pituitary-adrenocortical (HPA) and sympathoadernomedulary (SAM) systems, resulting in the elevation of blood pressure, heart rate, and circulating catecholamines and glucocorticoids. The patterns of autonomic, neuroendocrine, and behavioral responses vary with the type of stress, the different

perceptions of stress by the subject, the extent of control on the stressful stimulus, and the active or passive coping mechanisms in response stress (Benarroch 2006). Stressor-induced activation of the HPA axis and the SAM results in a series of neural and endocrine adaptations known as the "stress response" or "stress cascade." The stress cascade is responsible for allowing the body to make the necessary physiological and metabolic changes required to cope with the demands of a homeostatic challenge (Miller et al., 2002). The strongest stressors produce specific and nonspecific responses. The specific stress responses alter an individual to the presence of the stressors, which involve neuroendocrine responses such as increased autonomic nervous system activity (Tsigos et al., 2005) (Gold et al., 1998). When faced with excessive stress, whether physical or emotional, a subject's adaptive responses attain a relatively stereotypic nonspecific nature, referred to by Selye as "the general adaptation syndrome." We now know that the adaptive responses have some specificity toward the stressor that generates them, which, however, is progressively lost as the severity of the stressor increases. The adaptive response of an individual to stress is determined by a multiplicity of genetic, environmental and developmental factors (Chrousos et al., 1992) and prenatal life, infancy, childhood and adolescence are critical periods characterized by increased vulnerability to stressors (Charmandari et al., 2005).

2.3.2 Regulation of the stress response

The orchestrated interplay of several neurotransmitter systems in the brain underlies the characteristic phenomenology of behavioral, endocrine, autonomic and immune responses to stress (Chrousos, 1998). Stress mediators such as adrenocorticotropic hormone, adrenaline and noradrenaline are subsequently released in specific patterns, reflecting the degree of HPA, adrenomedullary, and sympathetic nervous system activation (Goldstein et al., 2008). All stress responses are centrally integrated in the paraventricular nucleus (PVN) of the hypothalamus (Herman et al., 1997 and 2008) and the adrenal glands are their major peripheral effectors (Goldstein et al., 2008). Hypophysiotropic CRH neurons of the PVN are well known to serve as the origin of the final common pathway of glucocorticoid secretion. The powerful and far reaching action of these steroids (including effects upon metabolic, inflammatory, immune functions and on mood and behavior) has led to intensive investigation into regulatory mechanisms controlling glucocorticoid secretion (Cullinan et al., 2000). This hypothalamic neurohormone (CRH) plays a central role in the regulation of the HPA-axis, i.e., the final common pathway in the stress response. The activation of CRH neurons, increasing both adrenocorticotropic hormone (ACTH) biosynthesis and the best marker in ACTH which reaches a maximum in the first hour, which cortisol is highest during the second hour of stress (Dobson et al., 2000). ACTH may play a crucial, perhaps direct, role in the regulation of catecholamine biosynthetic enzymes in sympathetic nervous system, especially during stress. CRH-R1 is the most abundant subtype found in the anterior pituitary and is also widely distributed in the brain (Wong et al., 1994). Other possible factors that may regulate CRH1 receptor mRNA expression in the PVN of rats are catecholamine and glucocorticoids. Regarding catecholaminergic regulation, studies show that brainstem hemi section, which damaged the ascending noradrenergic bundle at least, attenuated the immobilization stress-induced increase in CRH1 receptor mRNA ipsilaterally in the PVN. This previous finding may reflect up-regulation of CRH1 receptor mRNA in the PVN by noradrenergic input from brainstem nuclei, such as the locus coerulus (LC), during stress (Fig.1)(Makino et al., 2002).

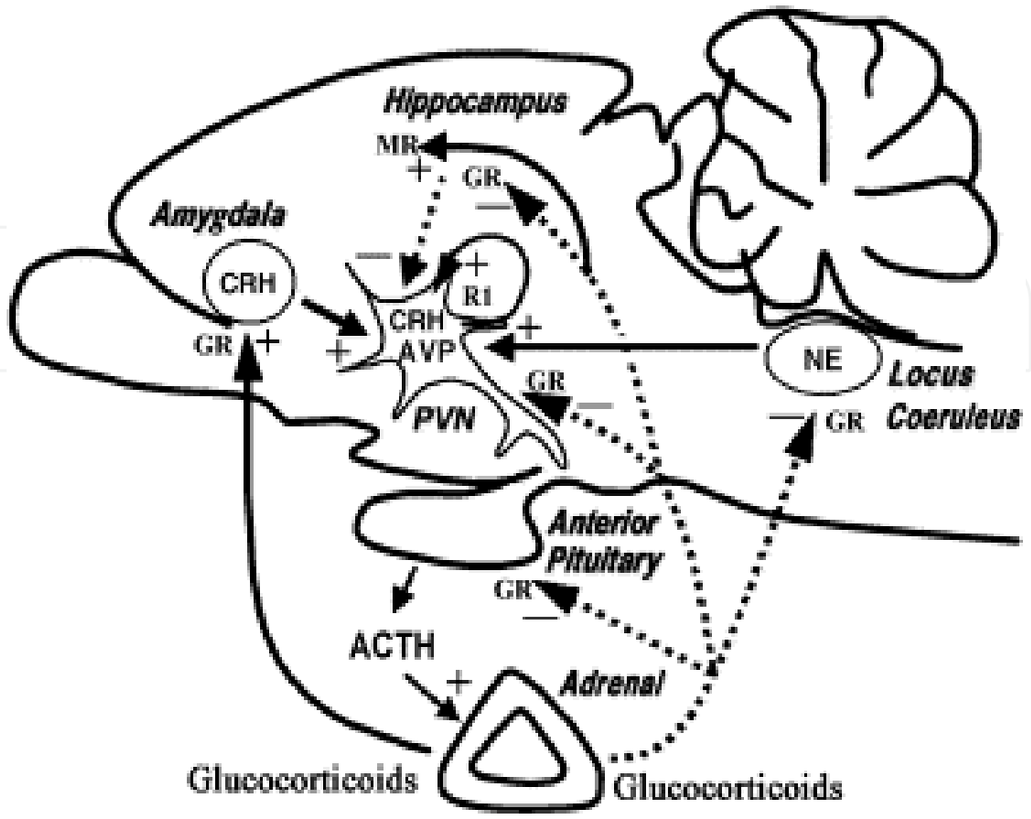


Fig. 1. Multiple feedback loops activating CRH systems during chronic stress. Stress initially activates the hypothalamic CRH system (i.e., CRH in the PVN), resulting in the hyper secretion of glucocorticoids from the adrenal gland. In addition, the psychological component of the stressor stimulates the amygdaloid CRH system (i.e., CRH in the central nucleus of the amygdala). Glucocorticoids exert GR-mediated negative feedback effects on the biosynthesis and release of CRH in the PVN and ACTH in the anterior pituitary (AP) directly or indirectly through the brainstem catecholaminergic nuclei such as the LC, resulting in the termination of stress-induced HPA axis activation. In the chronic phase of stress, down-regulation of GR in the PVN and other brain structures such as the LC fails to restrain hyper function of the HPA axis. Increased CRH in the PVN also induces a putative ultra short positive feedback effects on its own biosynthesis through up-regulation of PVN CRHr-1. The persistent activation of the HPA axis further up-regulates the amygdaloid CRH system involved in the expression of fear and anxiety, and the amygdala may have stimulatory effects on the HPA axis. Thus, the hypothalamic and the amygdaloid CRH systems cooperatively constitute stress-responsive, anxiety-producing neurocircuitry during chronic stress (Makino et al., 2002).

3. Overview of the HPA axis

3.1 Historical context of HPAC

In 1936, Hans Selye reported a historic series of studies on severe stress in rats. Exposure to bacterial infection, toxic chemicals, and other life threatening insults consistently caused

adrenal gland enlargement with high levels of corticosterone secretion, atrophy of the immune organs, and gastric ulcers. All three components of this nonspecific stress response are caused by prolonged activation of corticosteroids in the hypothalamic-pituitary-adrenal axis (HPAC), resulting in secretion of stress levels of ACTH and glucocorticoids. In spite of these harmful effects, glucocorticoids in normal levels are necessary for sustaining life (Munck et al., 1984). Here we discuss the key elements of the HPA axis and the neuroendocrine response to systemic and local stress.

3.2 HPA axis-CRH (homeostatic balance)

CRH, synthesized in the PVN of the hypothalamus, represents the main driving force controlling HPA axis activation, the major hormone system responsible to maintain homeostatic balance in response to stressful stimuli (Tsigos et al., 1994).

3.2.1 HPA axis & CRH: Response to systemic stress

The HPA axis originates from the CRH neurons in the parvocellular subdivision of the PVN of hypothalamus, while the sympathetic nervous system is under the regulation of brainstem locus coeruleus (LC), clustered with noradrenaline neurons. Morphological and immunocytochemical studies have demonstrated that reciprocal projections exist between PVN–CRH neurons and LC–NE neurons, forming a CRH–NE–CRH loop, which plays an important role in the stressful responses (Maier, 2003) (Pacak et al., 1998) (Pacak et al., 1995). Central CRH, via glucocorticoids and catecholamines, inhibits the inflammatory reaction, while directly secreted by peripheral nerves CRH stimulates local inflammation (immune CRH) (Tsigos et al., 2002). The gene for CRH is expressed, not only in the brain, but also in extracranial tissues, (Orth, 1992) (Owens et al., 1991) including normal mammalian skin (Slominski et al., 1995) (**a**Slominski et al., 1993) (bSlominski et al., 1993) (Ermak et al., 1997) (Slominski et al., 1998). It has been proposed that an equivalent to the hypothalamic-pituitary-adrenal axis functions in mammalian skin, in response to local stress (**a**Slominski et al., 1996).

3.2.2 HPA axis & CRH: Response to local stress

It has been known for several years that the CRH/ POMC skin system fulfils analogous (pro-opiomelanocortin) functions to the HPA stress axis. CRH is the central trigger of HPA axis, and together with related peptides urocortin I–III that are the most important elements of the body response to stress. These elements regulate behavioral, autonomic, endocrine, reproductive, cardiovascular, gastro-intestinal, metabolic and immune systemic functions (Aguilera et al., 2001) (Grammatopoulos et al., 2002). Other actions of CRH include local immunomodulatory (predominantly proinflammatory) effects (Karalis et al., 1991) (Slominski et al., 2003), differing from a central immunosuppressive activity (through the HPA axis) (Chrousos 1995). Moreover, expression of CRH and regulated activity of CRH receptor type 1 (CRH1) can also play an important role in regulation of local stress response in peripheral tissues including skin, gastrointestinal tract or reproductive system. In humans, expression of at least eight variants of CRH1 mRNA (α, β, c, d, e, f, g and h) was detected and alternative splicing was found to be regulated by diverse physiological and

pathological factors including: growth conditions, onset of labor during pregnancy or exposure to ultraviolet irradiation (Michal et al., 2010). Of note, locally produced CRH can directly regulate steroid hormone production by adrenals and gonads. Furthermore, CRH in the immune cells can induce production and release of POMC derived ACTH and beta-endorphin peptides. In vertebrates these peptides interact with membrane-bound CRH-R1 and CRH-R2 (Grammatopoulos et al., 2002) (Hillhouse et al., 2002). Both receptor types belong to the group II subfamily of G protein-coupled receptors (GPCRs). In human skin, CRH-R1 is the major receptor, expressed in both epidermal, dermal and subcutis with CRH-R1α being the most prevalent isoform. The CRH-R2 gene was expressed solely in hair follicle keratinocytes and papilla fibroblasts, whereas CRH-R2 antigen was localized predominantly in hair follicles, sebaceous and eccrine glands, muscle and blood vessels (**a**Slominski et al., 2004). A hair follicle is a typical stress-responding mini organ with a peculiar immune system. The proximal epithelium of an anagen hair follicle is known to be an area of immune privilege within the hair follicle immune system, whose collapse may be crucial for the pathogenesis of alopecia areata (Christoph et al., 2000).

3.3 HPA axis–immune system interactions

It has been known for several decades that stress, whether inflammatory, traumatic or psychological, is associated with concurrent activation of the HPA axis. In the early 1990s, it also became apparent that cytokines and other humoral mediators of inflammation are potent activators of the central stress response, constituting the afferent limb of a feedback loop through which the immune/inflammatory system and the CNS communicate (Chrousos 1995). All three inflammatory cytokines, tumor necrosis factor-(TNF), interleukin-1β and interleukin-6 (IL-6) can cause stimulation of the HPA axis alone, or in synergy with each other (Chrousos, 1995) (Tsigos et al., 1997). There is evidence to suggest that IL-6, the main endocrine cytokine, plays the major role in the immune stimulation of the axis, especially in chronic inflammatory stress. Some of the activating effects of cytokines on the HPA axis may be exerted indirectly by stimulation of the central catecholaminergic pathways. Conversely, activation of the HPA axis has profound inhibitory effects on the inflammatory/immune response because virtually all the components of the immune response are inhibited by cortisol. Alterations of leukocyte traffic and function, decreases in production of cytokines and mediators of inflammation, and inhibition of the latter's effects on target tissues are among the main immunosuppressive effects of glucocorticoids (Chrousos, 1995) (Elenkov, 1999).

3.4 HPA: The field of psychoneuroimmunology

Studies on stress-associated immune dysregulation have interested scientists and clinicians in the field of psychoneuroimmunology (PNI). This field focuses on the interactions among the central nervous system (CNS), the endocrine system and the immune system, and the impact these interactions have on health. Modulation of the immune response by the CNS is mediated by a complex network of signals that function in bi-directional communication among the nervous, endocrine and immune systems. HPA and SAM axes are the two major pathways through which immune function can be altered. The efferent sympathetic/adrenomedullary system apparently participates in a major fashion in the

interactions of the HPA axis and the immune/inflammatory reaction by being reciprocally connected with the CRH system, by receiving and transmitting humoral and nervous immune signals from the periphery, by densely innervating both primary and secondary lymphoid organs, and by reaching all sites of inflammation via the postganglionic sympathetic neurons. When activated during stress, the autonomic system exerts its own direct effects on immune organs, which can be immunosuppressive, or both immunopotentiating and antiinflammatory. CRH secreted by postganglionic sympathetic neurons at inflammatory sites has proinflammatory properties (immune *CRH*); one of its key actions is to degranulate mast cells (Elenkov, 1999).

4. Overview of skin

4.1 Skin (epidermal barrier homeostasis)

The epidermis and its array of appendages undergo ongoing renewal by a process called homeostasis. Stem cells in the epidermis have a crucial role in maintaining tissue homeostasis by providing new cells to replace those that are constantly lost during tissue turnover or following injury (Blanpain et al., 2009). A homeostatic process involved in the maintenance of an internal steady state within a defined tissue of an organism, including control of cellular proliferation and death(apoptosis) and control of metabolic function. Mammalian epidermis is a stratified epithelium that retains the ability to self renews under both homeostatic and injury conditions by maintaining a population of mitotically active cells in the hair follicles and innermost basal layer (Niemann et al., 2002) (Ito et al., 2005). The basic mechanisms and signalling pathways that orchestrate epithelial morphogenesis in the skin have been designed for protective effect of this organ. The stratum corneum is the outermost of the 5 layers of the epidermis and is largely responsible for the vital barrier function of the skin. The physical barrier localized primarily in the stratum corneum and consists of protein-enriched cells (corneocytes with cornified envelope and cytoskeletal elements, as well as corneodesmosomes) and lipid-enriched intercellular domains. The nucleated epidermis, with its tight, gap and adherens junctions, additional desmosomes and cytoskeletal elements, also contributes to the barrier. Lipids are synthesized in the keratinocytes during epidermal differentiation and are then extruded into the extracellular domains, where they form lipid-enriched extracellular layers (Jensen et al., 2009). Activation of HPA axis with release of stress neuropeptides is essential for biological homeostasis and responses to external and internal challenges (Lotti et al., 1999) (**b**Slominski et al., 1996).

4.2 Skin – Neuroendocrine organ

More than ten years ago a comprehensive model of the skin acting as neuroendocrine organ has been proposed (Milstone et al., 1988) (**a**Slominski et al., 2000). For example, the skin synthesizes vitamin D, which enters the circulation and, upon activation, exerts profound metabolic and endocrine effects (Kragballe et al., 1996). Although the concept is still evolving, it relies on the skin capacity to communicate with the central system and to regulate global homeostasis through local production and/or systemic release of classical hormones, neuropeptides, neurotransmitters and biological regulators (**b**Slominski et al., 2000).

4.3 Skin – Local stress (neuroendocrine activity)

Skin as a neuroendocrine organ, is a relatively new addition to the field of cutaneous biology; it combines concepts from immunology, endocrinology, and neurobiology to unravel the multidirectional communications between brain, the endocrine and immune systems, and peripheral organs (Blalock, 1989) (Pennisi, 1997) (Turnbull et al., 1999). In this regard, the skin has a unique role because of its location, size, and relative functional diversity. Moreover, cutaneous signals sent to neuroendocrine centers may play modulatory roles, although peripheral intraorgan or inter systemic communications are also necessary to maintain global and local homeostasis. Thus precise stress-response coordination is an additional cutaneous function that appears to be served by locally expressed neuroendocrine activities (**a**Slominski et al., 2000) (**b**Slominski et al., 2000) (Slominski et al., 2001).

4.4 Skin – Stress neuropeptides

CRH/CRH-R1 system: Is it a cutaneous HPA system?

Slominski and colleagues have extensively documented the nature of peripheral CRH, its receptors and their distribution in human and murine skin. They confirmed that skin stress–response system was coordinated by a local cutaneous HPA axis-like system. They demonstrated that CRH, its receptors, the related neuropeptide urocortin and pro-opiomelanocortin-derived peptides are expressed locally in normal skin, normal cycling hair follicle epithelium, benign and malignant melanocytic lesions and non-melanoma skin cancer (**b**Slominski et al., 2004). Corresponding functional receptors (CRH-R) in the same cells confirm paracrine or autocrine modes of action. In human skin, CRH-R1 mediates most phenotypic effects of CRH (Slominski et al., 2001) while the main adnexal location of CRH-R2 indicates a role for this receptor in hair cycling (Kauser et al., 2006). Then a localized circuit regulates the peripheral functions of cutaneous CRH/CRH-R1, and the aberrant expression of CRH/CRH-R1 in the skin disturbs the local homeostasis and leads to abnormal differentiation and proliferation in keratinocytes. Because of the aberrant terminal differentiation of keratinocytes, psoriatic plaques have scale on the surface, which breaks in the protective barrier (Bowcock et al., 2005). However, dysfunction of keratinocytes may decrease CRH/CRH-R1 expression because of disharmony in differentiation and proliferation of keratinocytes. Zhou et al., in 2009 found a significant detuning CRH/CRH-R1 system in psoriatic lesions, which suggests that an aberrant cutaneous HPA system might take part in the pathogenesis of psoriasis, especially the formation of plaque. Thus, they hypothesize that a cutaneous CRH/CRH-R1 system might be aberrant in lesions of psoriasis. The detuning of CRH/CRH-R1 regulation might contribute to the formation of plaque in psoriasis (zhou et al., 2009) (Slominski et al., 2005) (Fig. 2).

POMC is a prohormone that produces various bioactive peptides via a series of enzymatic steps in a tissue-specific manner, including ACTH, α-melanocyte stimulating hormone (α-MSH), and β-endorphin. POMC is expressed not only in the pituitary gland, but also in a variety of non-pituitary organs, including the skin (Millington 2006). The production of POMC peptides in keratinocytes and melanocytes was found to be under regulatory control (Schauer et al., 1994) being stimulated by UVB, selected cytokines, and by disease processes(Slominski et al., 1996**c**, 1998, 1993**a**, 1993**b**)(Chakraborty et al., 1996) (Winzen et al. 1996)(Wakamatsu et al., 1997).

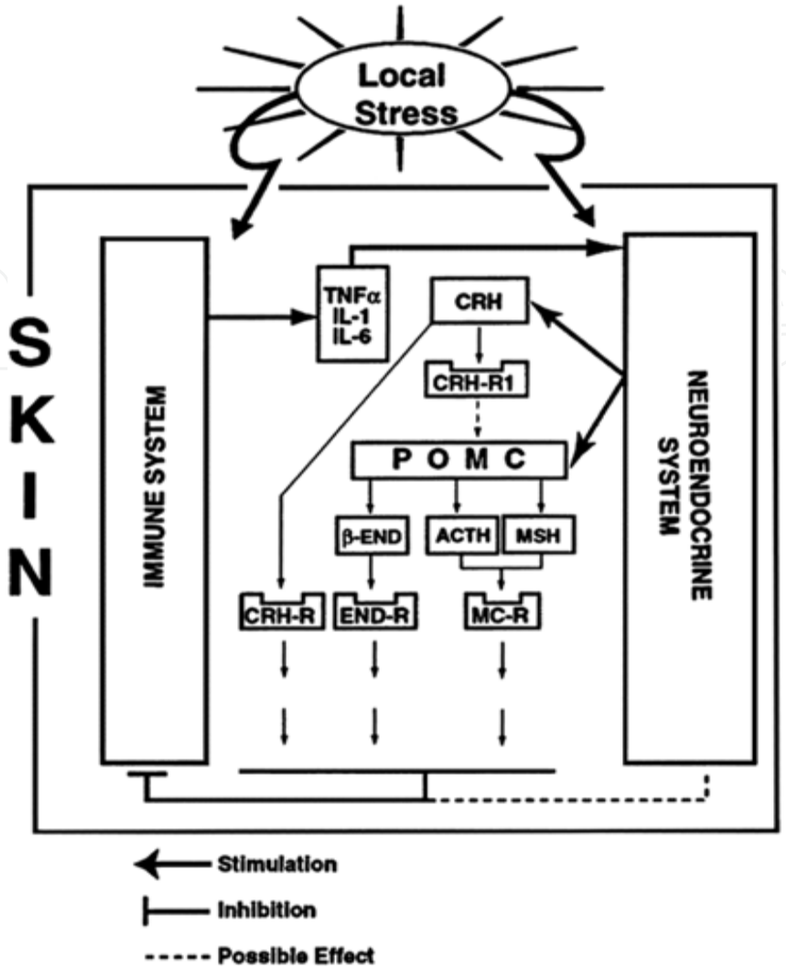


Fig. 2. The skin SNS are mediated via production of CRH and POMC peptides, and modulated by the local skin immune system (SIS). Signals originating in the latter and represented by proinflammatory cytokines perhaps stimulate production of CRH and POMC peptides. In turn, the signals generated by the interaction of CRH, ACTH, MSH, and β-endorphin, with their corresponding receptors, counteract the effect of local stress (Slominski et al., 2006).

4.5 Skin – The field of psychoneuroimmunology

Studies have shown that stress diminishes vaccine responses, exacerbates viral and bacterial pathogenesis, slows wound healing and alters autoimmune diseases (McCabe et al., 2000) (Padgett et al., 1998) (Teunis et al., 2002) (Dowdell et al., 1999). Because lymphocytes, monocytes or macrophages and granulocytes, exhibit receptors for many neuroendocrine products of the HPA and SAM axes, such as cortisol and catecholamines, which can cause changes in cellular trafficking, proliferation, cytokine secretion, antibody production and cytolytic activity .These studies have demonstrated that stress hormones inhibit the trafficking of neutrophils, macrophages, antigen-presenting cells, natural killer (NK) cells and T and B lymphocytes, suppress the production of proinflammatory cytokines and chemokines, downregulate the production of cytokines necessary for the generation of

adaptive immune responses and impair effector functions of macrophages, NK cells and lymphocytes. For example, treatment of peripheral blood leukocytes (PBLs) with catecholamines *in vitro* results in the suppression of interleukin-12 (IL-12) synthesis and an increase in IL-10 production (Elenkove et al., 1996). Data from both human and animal studies show that the connections between the neuroendocrine system and immune system provide a finely tuned regulatory system required for health. However, the immune cells and cytokines influencing keratinocyte function play a major role in the development and pathogenesis of psoriasis.

5. Overview of psoriasis

5.1 Psoriasis – Genetic

It is generally accepted that the genetic background for psoriasis susceptibility is pivotal for the appearance of the symptoms. Intensive family studies since the early 1950s and linkage analysis studies pointed out several genetic loci that play a role in psoriasis (Bhalerao et al., 1998). In the last decade, a molecular biology approach emerged to identify abnormally expressed genes and proteins contributing to psoriasis (Jackson et al., 1999) (Chen et al., 2000). Two major genes under investigation are IL12B on chromosome 5q, which expresses interleukin-12B; and IL23R on chromosome 1p, which expresses the interleukin-23 receptor, and is involved in T cell differentiation. T cells are involved in the inflammatory process that leads to psoriasis. These genes are on the pathway that ends up upregulating tumor necrosis factor-α and nuclear factor κB, two genes that are involved in inflammation (Nestle et al., 2009). Genome-wide association studies have also identified several new genomic loci, and compelling evidence has shown an interaction between the HLA-C and ERAP 1 loci, implicating pathways that integrate epidermal barrier dysfunction with innate and adaptive immune dysregulation in psoriasis (Strange et al., 2010).

5.2 Psoriasis – Keratinocytes

Psoriasis is a chronic inflammatory disease characterized by epidermal keratinocytic hyper proliferation and abnormal differentiation (Abdou et al., 2008). The upper most layer of skin, the epidermis, consists primarily of keratinocytes (>90% of all epidermal cells) (Sun et al., 1979). The keratin intermediate filament network is responsible for the extremely high keratinocyte stiffness and resilience. This could manifest into the rugged protective nature of the human epidermis (Lulevich et al., 2010). Therefore, keratinocytes form an effective barrier to the entry of protein antigens, chemical irritants, and infectious agents in to the body (Fuchs 1995), all while resisting environment stress, external pressure, and sheer force. The trigger of the keratinocyte response is thought to be activation of the cellular immune system, with T cells, dendritic cells and various immune-related cytokines and chemokines implicated in pathogenesis (Lowes et al., 2007).

5.2.1 Keratinocytes – Dendritic & T cells

Researchers have identified many of the immune cells involved in psoriasis, and the chemical signals they send to each other to coordinate inflammation. The immune system consists of an innate immune system, and an adaptive immune system. In the innate system, immune cells have receptors that have evolved to target specific proteins and other antigens

which are commonly found on pathogens. In the adaptive immune system, immune cells respond to proteins and other antigens that they may never have seen before, which are presented to them by other cells. The immune cells, such as dendritic cells (Dendritic cells are present in tissues in contact with the external environment, such as the skin: Once activated, they migrate to the lymph nodes where they interact with T cells and B cells to initiate and shape the adaptive immune response) and T cells, move from the dermis to the epidermis, secreting chemical signals, such as tumor necrosis factor-α, interleukin-1β, and interleukin-6, which cause inflammation, and interleukin18, 22 which causes keratinocytes to proliferate (Banchereau et al., 1998) (Nestle et al., 2009). Recent studies indicate that various cytokines play an essential role in the induction and maintenance of psoriatic lesion.

5.2.2 Keratinocytes – Cytokines

Various inflammatory cytokines and growth factors have been shown to be strongly induced in keratinocytes in psoriatic lesion. Although it is thought that the induction of cytokine production is the consequence of the activation of infiltrating immune cells rather than a triggering factor for the inflammatory process (Lowes et al., 2007). Three types of cytokines elaborated by keratinocytes are of particular interest in this context: growth factors for keratinocytes, endothelial cells and neutrophil-attracting chemokines. Several growth factors are able to induce keratinocyte proliferation and have been found to be highly expressed in lesional psoriatic epidermis. Transforming growth factor *a* (Elder et al., 1989) (Addison et al., 2010) and amphiregulin-epidermal growth factor (Cook et al., 1992) have been shown to induce epidermal proliferation and reproduce some aspects of the psoriatic phenotype when expressed in epidermal keratinocytes in transgenic animals (Cook et al., 1999) (Vassar et al., 1991). The epidermal growth factor (EGF) receptor ligand amphiregulin (AREG) has been implicated as an important autocrine growth factor in several epithelial malignancies and in psoriasis, a hyperproliferative skin disorder. In vitro, in vivo and clinical studies are well established the role of growth factors and neuropeptides in cutaneous innervation and there is substantial evidence that sensory neuropeptides contribute to the development of psoriasis (Saraceno et al., 2006).

5.2.3 Keratinocytes & peripheral CRH/CRH-R1

CRH is a central component of the local HPA axis, which has a functional equivalent in the skin. The ability of CRH to activate mast cells may explain its proinflammatory actions and the pathophysiology of certain skin conditions, which are precipitated or exacerbated by stress, such as atopic dermatitis, eczema, psoriasis, and urticaria (Theoharides et al., 1998). Mast cells are derived from stem cells in the bone marrow and migrate into tissues where they are prominently located just below the dermal–epidermal junction; they mature, depending on the tissue, under the influence of stem cell factor (SCF), interleukin 3 (IL-3), IL-4 and IL-9 (Wedemeyer et al., 2000). Mast cell infiltration and/or proliferation in the skin can be triggered by SCF released from fibroblasts and other immune cells, nerve growth factor (NGF) released from nerve endings, or RANTES (regulated on activation, normal T cells, expressed and secreted) (Conti et al., 1998) . Mast cells can also secrete SCF (de Paulis et al., 1999) and NGF (Xiang et al., 2000), thus affecting their own growth and activation (Gagari et al., 1997). The cytokines expressed by mast cells are primarily pro-inflammatory or are necessary for innate immunity [e.g. IL-1, IL-6, IL-8 and

tumor necrosis factor α (TNF-α) (Wedemeyer et al., 2000). Human mast cells were recently shown to be particularly rich in both CRH and the structurally related peptide urocortin (Ucn) (Kempuraj et al., 2004) and express multiple CRH receptor isoforms which suggests autocrine actions of CRH(Cao et al., 2003).

5.2.4 Keratinocytes – CRH & Mast cells

Skin and hypothalamic mast cells appear to have important physiological functions as sensors of stressful events with bidirectional regulation of the HPA axis; a local increase of the levels of CRH or Ucn in extracranial tissues under stress could adversely affect different disease states (Theoharides et al., 1998). Hypothalamic mast cells are located close to nerve endings that contain CRH and can be activated by acute stress (Rozniecki et al., 1999). Acute stress can trigger mast cell degranulation (Singh et al., 1999) and increased the number of skin mast cells and also can worsened delayed hypersensitivity, effects blocked by pretreatment with a CRH receptor antagonist (Kaneko et al., 2003). Neuropeptides can also activate mast cells in a receptor-independent manner by activating G proteins directly. Regardless of the mechanism of activation, mast cell-derived vasoactive, pro-inflammatory and neurosensitizing molecules could act on keratinocytes, endothelial cells or nerve endings to liberate additional molecules and lead to chronic inflammation and neuropathic hypersensitivity or pain. The Kempuraj et al., findings indicate that mast cells are not only the target, but also a potential source of CRH and Ucn that could have both autocrine and paracrine functions, especially in allergic inflammatory disorders (Kempuraj et al., 2004), atopic dermatitis and psoriasis exacerbated by stress (Theoharides et al., 2004).

5.2.5 Keratinocytes – CRH & Stress

The study of Mitsuma et al., in 2001 showed that CRH induces the proliferation of keratinocytes via interaction with CRH receptors (Mitsuma et al, 2001) and it may indicate the possible correlation of the proliferation of keratinocytes and the degree of stress. Therefore, activation of the stress system, via the direct and indirect effects of CRH, might affect the susceptibility of an individual to certain autoimmune, allergic, infectious, inflammatory or neoplastic diseases (Arbiser et al, 1999). The biological effects of CRH have been shown to include the inhibition of keratinocyte proliferation and regulation of adhesion molecules and cytokines (**c**Slominski et al, 2000)(Pisarchik et al., 2001)(Quevedo et al, 2001)(Zbytek et al, 2002). Dysregulation of the HPA and SAM systems has been proposed as one possible underlying cause of stress-induced flares of psoriasis (Heller et al., 2011).

5.3 Psoriasis & stress

Generally, in normal individuals, stress elevates stress hormones (i.e., increases cortisol levels). However, according to available studies, exposure to stress in psoriatic patients has been associated with diminished HPA responses and upregulated sympathic adernomedullary (SAM) responses (Richards et al., 2005). Evers et al., found psoriasis patients had significantly lower cortisol levels at moments when daily stressors are at peak levels. The study also reported that psoriasis patients with overall high levels of daily stressors exhibited lower mean cortisol levels, as compared to psoriatics with overall low levels of daily stressors (Evers et al., 2010) (Zangeneh et al., 2008). These blunted HPA

axis and elevated SAM system responses to stress may be crucial in better understanding the inflammatory characteristics of psoriasis, particularly in stress-responders. For instance, decreased secretion of cortisol and increased levels of epinephrine (Zangeneh et al., 2008) and norepinephrine may stimulate the release of mast cells, affect skin barrier function, and upregulate proinflammatory cytokines, which could thereby maintain or exacerbate psoriasis severity (Evers et al., 2010). Some authors have commented that this decreased cortisol response may be similar to how psoriasis flares with steroid withdrawal, as evidenced by the well known phenomena of steroid-induced psoriasis rebound (Richards et al., 2005).

5.3.1 Psoriasis & steroidogenic capabilities of keratinocytes

Glucocorticoids are essential for maintaining barrier competency, as exemplified in $GR^{-/-}$ mouse, where loss of GR function led to incomplete epidermal stratification, hyperproliferation and abnormal differentiation (Bayo et al., 2008). In addition, the cortisol analogue dexamethasone has been shown to acutely influence expression of genes regulating cell proliferation, differentiation, apoptosis and inflammation in primary human keratinocytes (PHK) (Elias 2005) (Stojadinovic et al., 2007). Accordingly, cortisol (hydrocortisone) is regarded as the most potent therapy for many inflammatory skin conditions including psoriasis and atopic dermatitis. Keratinocytes contain an abundance of cholesterol, the precursor to all steroids, as they are capable of synthesizing cholesterol de novo (Menon et al., 1985). Additionally, the cholesterol transporter, steroidogenic acute regulatory (StAR) protein has been identified in human epidermis by immunofluorescence histochemistry (**b**Slominski, et al., 2004) (Tuckey 2005). Evers's study in 2010 is the first longitudinal study of patients with psoriasis to show a relationship between cortisol levels and daily stressors, these results suggest that patients who continuously experience higher levels of daily stressors are characterized by persistently lower cortisol levels and might thus be more vulnerable to the effects of stress on their disease (Everse et al., 2010). Hannen et al., in 2011 demonstrated that primary human Keratinocytes (PHK) express all the elements required for cortisol steroidogenesis and metabolite pregnenolone through each intermediate steroid to cortisol. They showed that normal epidermis and cultured PHK express each of the enzymes (CYP11A1, CYP17A1, 3βHSD1, CYP21 and CYP11B1) that are required for cortisol synthesis. Collectively these data show that PHK are capable of extra-adrenal cortisol synthesis, which could be a fundamental pathway in skin biology with implications in psoriasis and atopic dermatitis (Hannen et al., 2011).

5.3.2 Psoriasis & stress axis

HPA axis is a critical adaptive system that maximizes survival potential in the face of physical or psychological challenge. The principal end products of the HPA axis, glucocorticoid hormones, act on multiple organ systems, including the brain, to maintain homeostatic balance. The brain is a target of stress, and the hippocampus is the first brain region, besides the hypothalamus, to be recognized as a target of glucocorticoids (Zangeneh et al., 2009). There is increasing evidence that the experience of stressful events is associated with the course of chronic inflammatory skin diseases. Buske-Kirschbaum et al., reported attenuated responsiveness of the HPA axis and further, an increased reactivity of the SAM system to stress in patients suffering from atopic dermatitis (AD) (Buske-Kirschbaum et al.,

2006) and psoriasis (Buske-Kirschbaum et al., 2010). It has been indicated that the redistribution of leukocytes in response to acute stress is mediated by the SAM, since adrenalectomy or blockade of β-adrenergic receptors has been found to mitigate this effect (Dhabhar et al., 1995) (Engler et al., 2004). It is widely accepted that the SAM system represents a major immunoregulatory system that controls various aspects of immunity (Sanders et al., 2002).

5.3.3 Psoriasis & SAM system: Aspect of psychoneuroimmunology

It has been suggested that a dysfunctional sympathoadernomedulatory (SAM) system may increase the risk of an aberrant immune response, especially under stressful conditions when the system is activated. In fact, altered leukocyte distribution to acute stress, for example, increased numbers of NK cells, monocytes, $CD4^+$ and $CD8^+$ cells have been reported in psoriasis patients (Schmid-Ott et al., 2001). Under non-pathological conditions, this process may optimize immunoprotection in the case of wounding or infection. However, in the psoriatic patient, leukocyte trafficking to the (chronically inflamed) skin has been found to be a major step in the development of psoriatic eruption (Mehlis et al., 2003). Thus, the finding of a stress-induced increase of leukocyte trafficking with a potentially increased influx of leukocytes into the skin could be of clinical significance, and could at least partly explain the often observed stress-induced exacerbation of psoriatic lesions. However, there is growing evidence that T cell mediated autoimmune processes and action of proinflammatory cytokines cause hyperproliferation of keratinocytes and assume the psoriatic phenotype (Krueger et al., 2005). When exposed to psychosocial stress, psoriasis patients showed increased monocyte and (activated) T cell number when compared to healthy controls. Further, a shift towards a TH_1-derived cytokine profile could be identified. These findings suggest that in psoriasis patient's stress may change immune functions towards a pathological relevant immune profile which could explain the often observed aggravation of psoriatic plaques in psoriasis patients under stressful conditions. Just as in many dermatologic conditions, psoriasis appears to worsen with stress in a significant segment of patients. For example, more than half of patients with psoriasis retrospectively report having experienced stressful life events before an exacerbation of the disease (Gupta et al., 1989) (Fortune et al., 1998). Studies report that the proportion of psoriasis patients who are "stress responders" ranges from 37% to 78% (Picardi et al., 2001).

5.3.4 Psoriasis & "stress responders"

Does stress cause or exacerbate psoriasis?

The answer is both, because the stress response disrupts physiological homeostasis and body function and contributes to disease production (Burchfield, 1979). This disruption of physiological homeostasis in the skin barrier is the trigger and stressors may contribute directly to the production of psoriasis disease or it contributes to the development of stress behavior, which increases the risk of disease. Stress has been indicated as a trigger in many dermatologic conditions and with each of these conditions, one encounters both patients who experience a close chronologic association between stress and exacerbation of their skin disease, and patients for whom their emotional states seem to be unrelated to the natural course of their cutaneous disorder. These two groups are considered "stress responders"

and "non-stress responders," respectively (Koo 1995). Psoriasis itself can serve as a stressor for patients. Psoriasis can be a disfiguring skin disease causing social stigma. Accordingly, patients often suffer significant interpersonal and psychological distress. Patients commonly experience difficulties in social interactions, especially in meeting new individuals and forming romantic relationships. In general, most patients demonstrate adverse psychological consequences, including poor self-esteem, anxiety, depression, and for some, even develop suicidal ideation (Russo et al 2004). As psoriasis can cause considerable stress for patients and increased levels of stress are likely to exacerbate psoriasis, the disease process, thus, becomes a self-perpetuating, vicious cycle (Kimball et al., 2005). Therefore, treatment considerations for psoriasis stress responders should integrate methods of psychotherapy and pharmacotherapy that can decrease stress.

6. References

Abdou AG, Hanout HM. Evaluation of survivin and NF–kappaB in psoriasis, an immunohistochemical study. J Cutan Pathol 2008; 35: 445–451.

Arbiser JL, Karalis K, Viswanathan A, Koike C, Anand-Apte B, Flynn E, Zetter B, Majzoub JA. Corticotropin-releasing hormone stimulates angiogenesis and epithelial tumor growth in the skin. J Invest Dermatol. 1999; 113: 838-42.

Aguilera G, Rabadan-Diehl C, Nikodemova M. Regulation of pituitary corticotropin releasing hormone receptors. Peptides. 2001; 22: 769–74.

Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature 1998; 392: 245–52.

Bayo P, Sanchis A, Bravo A, Cascallana JL, Buder K, Tuckermann J, Schütz G, Pérez P. Glucocorticoid receptor is required for skin barrier competence. Endocrinology. 2008;149: 1377-88.

Benarroch EE. (2006). Basic Neurosciences with Clinical Applications. Mayo Foundation for Medical Education and research. United States of America, Chap: Central control of homeostasis and adaptation, pp:761and 769.

Bhalerao J, Bowcock AM. The genetics of psoriasis: A complex disorder of the skin and immune system. Hum Mol Genet. 1998; 7: 1537-1545.

Blalock JE. Molecular basis for bidirectional communication between the immune and the neuroendocrine systems. Physiol Rev. 1989; 69:1–32.

Blanpain C, Fuchs E. Epidermal homeostasis: a balancing act of stem cells in the skin. Nat Rev Mol Cell Biol. 2009; 10: 207–217.

Bernard C. (1927). An introduction to the study of experimental medicine.1949, (2nd Ed.). New York: H.C. Greene.

Bowcock AM, KruegerJG. Getting under the skin: the immunogenetics of psoriasis. Nature Rev. 2005; 5: 699–711.

Burchfield SR. The evolution of the stress response: A new perspective. Psychosom-Med. 1979; 41,661.

Buske-Kirschbaum A, Ebrecht M, Kern S, et al. Endocrine stress responses in TH1-mediated chronic inflammatory skin disease (psoriasis vulgaris)--do they parallel stress-induced endocrine changes in TH2-mediated inflammatory dermatoses (atopic dermatitis)? Psychoneuroendocrinology 2006; 3: 439-46.

Buske-Kirschbaum A, Kern S, Ebrecht M, Hellhammer DHAltered distribution of leukocyte subsets and cytokine production in response to acute psychosocial stress in patients with psoriasis vulgaris. Brain, Behavior, and Immunity 2007; 21: 92-99

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, Behavior, and Immunity 2010; 24: 1347-1353.

Cannon W B. (1939). The Wisdom of the Body. New York: W.W. Nortyon and Co.

Cao J, Zhao P, Zhao LJ, Wu SM, Zhu SY, Qi ZT. Identification of functional corticotropin-releasing hormone (CRH) receptor isoforms in human leukemic mast cells (HMC-1), Mol. Biol. Cell 2003; 14: L212.

Chakraborty AK, Funasaka Y, Slominski A, Ermak G, Hwang J, Pawelek JM, Ichihashi M. Production an release of proopiomelanocortin (POMC)-derived peptides by human melanocytes and keratinocytes in culture: Regulation by UVB. Biochim. Biophys. Acta 1996; 1313: 130–138.

Charmandari E, Tsigos C, Chrousos G. Endocrinology of stress response. Annual Review of Physiology 2005; 67: 259-284.

Chen SH, Arany I, Apisarnthanarax N, Rajaraman S, Tyring SK, Horikoshi T, Brysk H, Brysk MM. Response of keratinocytes from normal and psoriatic epidermis to interferon-gamma differs in the expression of zinc-alpha (2)-glycoprotein and cathepsin D. Faseb J. 2000 ; 14: 565-71.

Christoph T, Müller-Röver S, Audring H, Tobin DJ, Hermes B, Cotsarelis G, Rückert R, Paus R.The human hair follicle immune system: cellular composition and immune privilege. Br J Dermatol. 2000; 142: 862-73.

Chrousos G.P., Gold P.W. The concepts of stress system disorders: overview of behavioral and physical homeostasis. JAMA, J Am Med Assoc. 1992; 267:1244–1252.

Chrousos GP. The hypothalamic– pituitary– adrenal axis and immune mediated inflammation. N Engl J Med. 1995; 332: 1351– 63.

Chrousos G P. Stressors, stress, and neuroendocrine integration of the adaptive response. The 1997 Hans Selye Memorial Lecture. Ann NY Acad Sc. 1998; 851: 311–335.

Conti P, Reale M, Barbacane RC, Letourneau R, Theoharides TC. Intramuscular injection of hrRANTES causes mast cell recruitment and increased transcription of histidine decarboxylase in mice: lack of effects in genetically mast cell-deficient W/WV mice. ASEB J. 1998; 12: 1693-700.

Cook PW, Pittelkow MR, Keeble WW, Graves-Deal R, Coffey Jr RJ, Shipley GD. Amphiregulin messenger RNA is elevated in psoriatic epidermis and gastrointestinal carcinomas. Cancer Res. 1992; 52: 3224–3227.

Cook PW, Pittelkow MR, Piepkorn M. Overexpression of amphiregulin in the epidermis of transgenic mice induces a psoriasis-like cutaneous phenotype. J Invest Dermatol. 1999; 113: 860.

Cullinan WE, Wolfe TJ. Chronic stress regulates levels of mRNA transcripts encoding beta subunits of the GABA(A) receptor in the rat stress axis. Brain Res. 2000; 887: 118-24.

Dhabhar FS, Miller AH, McEwen BS, Spencer RL. Effects of stress on immune cell distribution. Dynamics and hormonal mechanisms. J Immunol. 1995 ;154(10) :5511-27.

de Paulis A, Minopoli G, Arbustini E, de Crescenzo G, Dal Piaz F, Pucci P, Russo T, Marone G. Stem cell factor is localized in, released from, and cleaved by human mast cells. J Immunol. 1999; 163:2799-808.

Devrimci-Ozguven H, Kundakci TN, Kumbasar H, et al. The depression, anxiety, life satisfaction and affective expression levels in psoriasis patients. J Eur Acad Dermatol Venereol 2000; 14: 267-71.

Dobson H, Smith RF. What is stress, and how does it affect reproduction. Anim Reprod Sci., 2000; 60-61: 743-52.

Dowdell KC, Gienapp IE, Stuckman S, Wardrop RM, Whitacre CC.Neuroendocrine modulation of chronic relapsing experimental autoimmune encephalomyelitis: a critical role for the hypothalamic-pituitary-adrenal axis. J Neuroimmunol. 1999; 100: 243-51.

Elder JT, Fisher GJ, Lindquist PB. Overexpression of transforming growth factor alpha in psoriatic epidermis. Science 1989; 243: 811–814.

Elenkov IJ, Papanicolaou DA, Wilder RL, Chrousos GP. Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: clinical implications. Proc Assoc Am Physicians. 1996; 108: 374-81.

Elenkov IJ, Webster EL, Torpy DJ, Chrousos GP. Stress, corticotropin-releasing hormone, glucocorticoids, and the immune/inflammatory response: acute and chronic effects. Ann NY Acad Sci. 1999; 876; 1– 11 (discussion 11-3).

Elias PM. Stratum corneum defensive functions: an integrated view. J. Invest. Dermatol. 2005; 125: 183–200.

Engler H, Dawils L, Hoves S, Kurth S, Stevenson JR, Schauenstein K, Stefanski V. Effects of social stress on blood leukocyte distribution: the role of alpha- and beta-adrenergic mechanisms. J Neuroimmunol. 2004 ;156(1-2):153-62.

Ermak G, Slominski A. Production of POMC, CRH-R1, MC1, and MC2 receptor mRNA and expression of tyrosinase gene in relation to hair cycle and dexamethasone treatment in the C57BL/6 mouse skin. J Invest Dermatol. 1997; 108: 160-5.

Evers AW, Verhoeven EW, Kraaimaat FW, de Jong EM, de Brouwer SJ, Schalkwijk J, Sweep FC, van de Kerkhof PC. How stress gets under the skin: cortisol and stress reactivity in psoriasis. Br J Dermatol. 2010; 163: 986-91.

Fortune DG, Richards HL, Main CJ, Griffiths CE. What patients with psoriasis believe about their condition? J Am Acad Dermatol. 1998; 39:196–201.

Fuchs E. Keratins and the skin. Annu Rev Cell Dev Biol. 1995; 11: 123-53.

Gagari E, Tsai M, Lantz CS, Fox LG, Galli SJ. Differential release of mast cell interleukin-6 via c-kit. Blood 1997; 89: 2654-63.

Gold PW, Chrousos GP. The endocrinology of melancholic and atypical depression: relation to neurocircuitry and somatic consequences. Proc Assoc Am Physicians. 1998; 111: 22–34.

Goldstein DS, Kopin IJ. Adrenomedullary, adrenocortical, and sympathoneural responses to stressors: a meta-analysis. Endocr Regul. 2008; 42: 111-9.

Grammatopoulos DK, Chrousos GP. Functional characteristics of CRH receptors and potential clinical applications of CRH-receptor antagonists. Trends Endocrinol Metab. 2002;13:436–44.

Gupta MA, Gupta AK, Kirkby S, et al. A psychocutaneous profile of psoriasis patients who are stress reactors. A study of 127 patients. Gen Hosp Psychiatry 1989; 11:166-73.

Hannen RF, Michael AE, Jaulim A, Bhogal R, Burrin JM, Philpott MP. Steroid synthesis by primary human keratinocytes; implications for skin disease. Biochem Biophys Res Commun. 2011;404: 62-7.

Heller MM, Lee ES, Koo JY. Stress as an influencing factor in psoriasis. Skin Therapy Lett. 2011 ; 16: 1-4.

Herman JP, Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci. 1997; 20: 78-84.

Herman JP, Flak J, Jankord R. Chronic stress plasticity in the hypothalamic paraventricular nucleus. Prog Brain Res. 2008; 170: 353-64.

Hillhouse EW, Randeva H, Ladds G, Grammatopoulos D. Corticotropin-releasing hormone receptors. Biochem Soc Trans. 2002 Aug;30(4):428-32.

Hippocrates. On airs, waters, and places. (1923); (translated by WHS Jones, New York). New York: W. Heinmann.

Ito M., et al. Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis. Nat. Med. 2005; 11: 1351–1354.

Jackson M, Howie SE, Weller R, Sabin E, Hunter JA, McKenzie RC. Psoriatic keratinocytes show reduced IRF-1 and STAT-1alpha activation in response to gamma-IFN. Faseb J. 1999; 13: 495-502

Jensen JM, Proksch E. The skin's barrier. Ital G.Dermatol Venereol. 2009; 144: 689-700.

Kaneko K, Kawana S, Arai K, Shibasaki T. Corticotropin-releasing factor receptor type 1 is involved in the stress-induced exacerbation of chronic contact dermatitis in rats. Exp Dermatol. 2003; 12: 47–52.

Karalis K, Sano H, Redwine J, Listwak S, Wilder RL, Chrousos GP. Autocrine or paracrine inflammatory actions of corticotropin-releasing hormone in vivo. *Science.* 1991; 254: 421–3.

Kastelan M, Massari LP, Brajac I. Apoptosis mediated by cytolytic molecules might be responsible for maintenance of psoriatic plaques. Med Hypotheses. 2006; 67: 336-7.

Kastelan M, Prpić-Massari L, Brajac I. Apoptosis in psoriasis. Acta Dermatovenerol Croat. 2009; 17: 182-6.

Kauser S, Slominski A, Wei ET, Tobin DJ. Modulation of the human hair follicle pigmentary unit by corticotropin-releasing hormone and urocortin peptides. Faseb J. 2006; 20: 882-95.

Kempuraj D, Papadopoulou NG, Lytinas M, Huang M, Kandere-Grzybowska K, Madhappan B, Boucher W, Christodoulou S, Athanassiou A, Theoharides TC. Corticotropin-releasing hormone and its structurally related urocortin are synthesized and secreted by human mast cells. Endocrinology 2004; 145: 43–48.

Kimball AB, Jacobson C, Weiss S, Vreeland MG, Wu Y. The psychosocial burden of psoriasis. Am J Clin Dermatol. 2005; 6: 383-92.

Koo JY. Psychodermatology: a practical manual for clinicians. Cur Prob Dermatol. 1995; 6: 204-32.

Kragballe K, Fogh K, Larsen CG. Vitamin D: actions and applications in dermatology. J Invest Dermatol Symp Proc. 1996; 1:1–114.

Krueger GG, Langley RG, Finlay AY, Griffiths CE, Woolley JM, Lalla D, Jahreis A. Patient-reported outcomes of psoriasis improvement with etanercept therapy: results of a randomized phase III trial. Br J Dermatol. 2005 ; 153: 1192-9

Kvetnansky R, Sabban EL, Palkovits M. Catecholaminergic systems in stress: structural and molecular genetics approaches. Physiol Rev. 2009; 89: 535-606.

Lebwolhl M. Psoriasis. Lancet. 2003; 361:1197–1204.

Lotti T, Bianchi B, Panconesi E. Neuropeptides and skin disorders. The new frontiers of neuro-endocrine-cutaneous immunology. International J Dermatol. 1999; 38: 673–675.

Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature. 2007;445: 866-73.

Lulevich V, Yang HY, Isseroff RR, Liu GY.Single cell mechanics of keratinocyte cells. Ultramicroscopy. 2010: 110: 1435-42.

McCabe PM, Sheridan JF, Weiss JM, Kaplan JP, Natelson BH, Pare WP. Animal models of disease. Physiol Behav. 2000; 68: 501-7.

Maier S F. Bi-directional immune-brain communication: Implications for understanding stress, pain, and cognition. Brain Behav. Immun. 2003; 17: 69–85

Makino S, Hashimoto K, Gold P W. Multiple feedback mechanisms activating corticotropin-releasing hormone system in the brain during stress. Pharmacol Biochem Behav. 2002; 73: 147-58.

Mehlis SL, Gordon KB. The immunology of psoriasis and biologic immunotherapy. J Am Acad Dermatol. 2003 ;49(2 Suppl): S44-50

Menon GK, Feingold KR, Moser AH, Brown BE, Elias PM. De novo sterologenesis in the skin. II. Regulation by cutaneous barrier requirements. J. Lipid Res.1985; 26: 418–427.

Michal A. Zmijewski and Andrzej T. Slominski. Emerging role of alternative splicing of CRF1 receptor in CRF signaling. Acta Biochim Pol. 2010; 57(1): 1–13.

Miller DB, O'Callaghan JP. Neuroendocrine aspects of the response to stress. Metabolism 2002; 51(6 Suppl 1): 5-10.

Millington GW, Proopiomelanocortin (POMC): the cutaneous roles of its melanocortin products and receptors. Clin Exp Dermatol. 2006; 31: 407–412.

Milstone LM, Edelson RL. Endocrine, metabolic and immunologic functions of keratinocytes. Ann NY Acad Sci 1988; 548:1–366.

Mitsuma T, Matsumoto Y, Tomita Y. Corticotropin releasing hormone stimulates proliferation of keratinocytes. Life Sci. 2001; 69: 1991-8.

Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocr Rev. 1984; 5: 25-44.

Naldi L, Gambini D. The clinical spectrum of psoriasis. Clin Dermatol. 2007;25:510–518.

Nestle FO, Kaplan DH, Barker J. Psoriasis. N. Engl. J. Med.2009; 361: 496–509.

Niemann C, Watt FM. Designer skin: lineage commitment in postnatal epidermis. Trends Cell Biol. 2002;12:185–192.

Orth, DN. Corticotropin-releasing hormone in humans. Endocrine Rev. 1992; 13: 164–191.

Owens, MJ, Nemeroff CB. Physiology and pharmacology of corticotropin releasing factor. Pharmacol. 1991; 43: 425–473.

Pacak K, Palkovits M, Kopin IJ, Goldstein DS. Stress-induced norepinephrine release in the hypothalamic paraventricular nucleus and pituitary-adrenocortical and sympathoadrenal activity: in vivo microdialysis studies. Front. Neuroendocrinol. 1995; 16: 89–150.

Pacak K, Palkovits M, Yadid G, Kvetnansky R, Kopin IJ, Goldstein DS. Heterogeneous neurochemical responses to different stressors: a test of Selye's doctrine of nonspecificity. Am. J. Physiol. 1998; 275: R1247–R1255.

Padgett DA, Marucha PT, Sheridan JF. Restraint stress slows cutaneous wound healing in mice. Brain Behav Immun. 1998 Mar;12(1):64-73.

Pennisi E. Tracing molecules that make the brain-body connection. Science 1997; 275:930–931.

Picardi A, Abeni D. Stressful life events and skin diseases: disentangling evidence from myth. Psychother Psychosom 2001; 70:118-36.

Pisarchik A, Slominski, A: Alternative splicing of CRH-R1 receptors in human and mouse skin: Identification of new variants and their differential expression. Faseb J. 2001; 15: 2754-2756

Quevedo ME, Slominski A, Pinto W, Wei E, Wortsman J. Pleiotropic effects of corticotropin releasing hormone on normal human skin keratinocytes. In Vitro Cell Dev Biol Anim. 2001; 37: 50-4.

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; 153: 1114-20.

Roznieckі JJ, Dimitriadou V, Lambracht-Hall M, Pang X, Theoharides TC. Morphological and functional demonstration of rat dura mast cell-neuron interactions in vitro and in vivo, Brain Res. 849 (1999), pp. 1–15.

Russo PA, Ilchef R, Cooper AJ. Psychiatric morbidity in psoriasis: a review. Australas J Dermatol. 2004; 45:155-9.

Sanders VM, Kohm AP. Sympathetic nervous system interaction with the immune system. Int Rev Neurobiol. 2002 ;52 :17-41.

Saraceno R, Kleyn CE, Terenghi G, Griffiths CE. The role of neuropeptides in psoriasis. Br J Dermatol. 2006 ;155: 876-82.

Schauer E, Trautinger F, Köck A, Schwarz A, Bhardwaj R, Simon M, Ansel JC, Schwarz T, Luger TA. Proopiomelanocortin-derived peptides are synthesized and released by human keratinocytes. J. Clin. Invest. 1994; 93: 2258–2262.

Schmid-Ott G, Jaeger B, Adamek C, Koch H, Lamprecht F, Kapp A, Werfel T. Levels of circulating CD8(+) T lymphocytes, natural killer cells, and eosinophils increase upon acute psychosocial stress in patients with atopic dermatitis. J Allergy Clin Immunol. 2001; 107: 171-7.

Selye H. A syndrome produced by diverse nocuous agents. Nature 1936; 138: 230−231.

Selye H. A syndrome produced by diverse nocuous agents. 1936, J. Neuropsychiatry Clin. Neurosci. 1998; 10: 230–231.

Singh LK, Pang X, Alexacos N, Letourneau R, Theoharides TC. Acute immobilization stress triggers skin mast cell degranulation via corticotropin releasing hormone, neurotensin and substance P: A link to neurogenic skin disorders, Brain Behav. Immun. 1999;13: 225–239.

aSlominski, A, Paus R, Wortsman J. On the potential role of proopiomelanocortin in skin physiology and pathology. Mol. Cell. Endocrinol. 1993; 93: C1–C6.

bSlominski A, Wortsman J, Mazurkiewicz JE, Matsuoka L, Dietrich J, Lawrence K, Gorbani A, Paus R. Detection of the proopiomelanocortin-derived antigens in normal and pathologic human skin. J. Lab. Clin. Med.1993; 122: 658–666.

aSlominski, A. Ermak G, Hwang J, Mazurkiewicz J, Corliss D, Eastman A . The expression of proopiomelanocortin (POMC) and of corticotropin releasing hormone receptor (CRH-R) genes in mouse skin. Biochim. Biophys. Acta 1996; 1289: 247–251.

bSlominski A, Mihm MC. Potential mechanism of skin response to stress. Int J Dermatol. 1996 ; 35: 849-51.

Slominski, A, Pawelek J. Animals under the sun: effects of ultraviolet radiation on mammalian skin. Clin. Dermatol.1998; 16: 503–515.

aSlominski A, Wortsman J. Neuroendocrinology of the skin. Endocr Rev. 2000; 21:457-87.

bSlominski 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: 979-1020.

cSlominski A, Szczesniewski A, Wortsman J. Liquid chromatography–mass spectrometry detection of corticotropin-releasing hormone and proopiomelanocortin-derived peptides in human skin, J Clin Endocrinol Metab. 2000; 85: 3582–3588.

Slominski A, Wortsman J, Pisarchik A, Zbytek B, Linton EA, Mazurkiewicz JE, and Wei ET. Cutaneous expression of corticotropin-releasing hormone (CRH), urocortin, and CRH receptors. Faseb J. 2001; 15: 1678–1693.

Slominski A, Wortsman J, Linton E, Pisarchik A, Zbytek B. The skin as a model for the immunodulatory effects of corticotropin-releasing hormone. In: Schäfer M, Stein C, editors. Mind over Matter - Regulation of Peripheral Inflammation by the CNS. Birkhäuser Verlag; Basel: 2003.

aSlominski A, Pisarchik A, Tobin DJ, Mazurkiewicz JE, Wortsman J. Differential expression of a cutaneous corticotropin-releasing hormone system. Endocrinology 2004; 145: 941–50.

bSlominski A, Zjawiony J, Wortsman J, Semak I, Stewart J, Pisarchik A, Sweatman T, Marcos J, Dunbar C, Tuckey RT. A novel pathway for sequential transformation of 7-dehydrocholesterol and expression of the P450scc system in mammalian skin. Eur. J. Biochem. 2004; 271: 4178–4188.

Slominski A, Zbytek B, Semak I, Sweatman T, Wortsman J. CRH stimulates POMC activity and corticosterone production in dermal fibroblasts. J Neuroimmunol. 2005: 162: 97–102.

Stojadinovic OP, Lee b, Vouthounis C, Vukelic S, Pastar I, Blumenberg M, Brem H, Tomic-Canic M. Novel genomic effects of glucocorticoids in epidermal keratinocytes: inhibition of apoptosis, interferon-gamma pathway, and wound healing along with promotion of terminal differentiation. J. Biol. Chem. 2007; 282: 4021–4034.

Strange A, Capon F, Spencer CC, et al. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet. 2010; 42: 985–990.

Sun TT, Shih C, Green H. Keratin cytoskeletons in epithelial cells of internal organs. Proc Natl Acad Sci U S A. 1979; 76: 2813-7.

Theoharides TC, Singh LK, Boucher W, Pang X, Letourneau R, Webster E, Chrousos G. Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. Endocrinology 1998 ;139: 403-13.

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; 25: 563-8.

Tsigos C, Chrousos G P. Physiology of the hypothalamic–pituitary–adrenal axis in health and dysregulation in psychiatric and autoimmune disorders. Endocrinol Metab Clin North Am.1994; 23:451–466.

Tsigos C, Papanicolaou DA, Kyrou I, Defensor R, Mitsiadis CS, Chrousos GP. Dose-dependent effects of recombinant human interleukin-6 on glucose regulation. J Clin Endocrinol Metab. 1997; 82: 4167–70.

Tsigos C, Kyrou I, Chrousos GP. (2005) Stress, endocrine manifestations, and diseases. In: Cooper CL. (ed.) Handbook of Stress, Medicine, and Health. 2nd Edition. Boca Raton FL: CRC Press.pp: 101 – 131.

Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res. 2002; 53: 865-71.

Teunis MA, Heijnen CJ, Sluyter F, Bakker JM, Van Dam AM, Hof M, Cools AR, Kavelaars A. Maternal deprivation of rat pups increases clinical symptoms of experimental autoimmune encephalomyelitis at adult age. J Neuroimmunol. 2002; 133: 30-8.

Tuckey RC. Progesterone synthesis by the human placenta, Placenta 2005; 26: 273–281. Vassar R, Fuchs E. Transgenic mice provide new insights into the role of TGF-alpha during epidermal development and differentiation. Genes Dev. 1991; 5: 714–727.

Turnbull AV, Rivier CL. Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. Physiol Rev. 1999; 79:1–71.

Verhoeven EW, Kraaimaat FW, de Jong EM, Schalkwijk J, van de Kerkhof PC, Evers AW. Individual differences in the effect of daily stressors on psoriasis: a prospective study. J Invest Dermatol. 2009; 129: 2075–7.

Wakamatsu K, Graham A, Cook D, Thody AJ. Characterization of ACTH peptides in human skin and their activation of the melanocortin-1 receptor. Pigment Cell Res. 1997; 10: 288–297.

Weatherhead SC, Farr PM, Jamieson D, Hallinan JS, Lloyd JJ, Wipat A, Reynolds NJ. Keratinocyte Apoptosis in Epidermal Remodeling and Clearance of Psoriasis Induced by UV Radiation. Invest Dermatol. 2011 May 26. [Epub ahead of print]

Wedemeyer J, Tsai M, Galli SJ. Roles of mast cells and basophils in innate and acquired immunity. Curr Opin Immunol. 2000; 12: 624-31.

Wintzen M, Yaar M, Burbach JP, Gilchrest BA. Proopiomelanocortin gene product regulation in keratinocytes. J. Invest. Dermatol. 1996; 106: 673–678.

Wong M, Licinio J, Pasternak K I, Gold P W. Localization of corticotropin- releasing hormone (CRH) receptor mRNA in adult rat brain by in situ hybridization histochemistry. Endocrinology 1994; 135: 2275– 8.

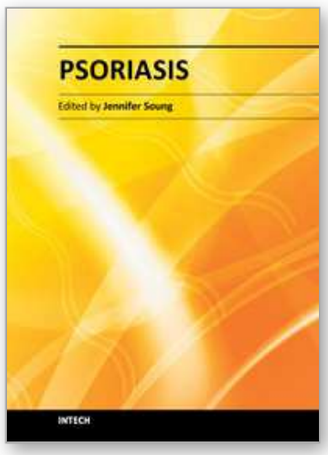
Xiang Z, Nilsson G. IgE receptor-mediated release of nerve growth factor by mast cells. Clin Exp Allergy. 2000; 30: 1379-86.

Zangeneh FZ, Fazeli A. The significance of stress hormones in psoriasis. Acta Medica Iranica 2008; 46: 485-488.

Zangeneh FZ، Shooshtary FS. Chronic Stress and Limbic-Hypothalamopituitary-Adrenal Axis (LHPA) Response in Female Reproductive system. Journal of Family and Reproductive Health 2009 ;3: 101-108.

Zbytek B, Mysliwski A, Slominski A, Wortsman J, Wei ET, Mysliwska J. Corticotropin-releasing hormone affects cytokine production in human HaCaT keratinocytes. Life Sci. 2002;70: 1013-21.

Zhou C, Yu X, Cai D, Liu C, Li C. Role of corticotropin-releasing hormone and receptor in the pathogenesis of psoriasis. Medical Hypotheses 2009; 73: 513-515.



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