

New approach to the understanding of keloid: psychoneuroimmune–endocrine aspects

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[†]Bernardo Hochman passed away on
April 21, 2014

Abstract: The skin is a dynamic and complex organ that relies on the interrelation among different cell types, macromolecules, and signaling pathways. Further, the skin has interactions with its own appendages and other organs such as the sebaceous glands and hair follicles, the kidney, and adrenal glands; systems such as the central nervous system; and axes such as the hypothalamic–pituitary–adrenal axis. These continuous connections give the skin its versatility, and when an injury is caused, some triggers start a cascade of events designed to restore its integrity. Nowadays, it is known that this psychoneuroimmune–endocrine intercommunication modulates both the homeostatic condition and the healing process. In this sense, the skin conditions before a trauma, whether of endogenous (acne) or exogenous origin (injury or surgical incision), could regulate the process of tissue repair. Most skin diseases such as psoriasis and atopic dermatitis, among others, have in their pathophysiology a psychogenic component that triggers integrated actions in the nervous, immune, and endocrine systems. However, fibroproliferative disorders of wound healing, such as hypertrophic scar and keloid, are not yet included in this listing, despite showing correlation with stress, especially with the psychosocial character. This review, by understanding the “brain–skin connection”, presents evidence that allows us to understand the keloid as a psychomediated disease.

Keywords: keloid, stress, psychological, psychoneuroimmunology, wound healing

Introduction

Keloid is considered a fibroproliferative disorder of skin wound healing, and its pathophysiological mechanisms are not fully known. As keloid only occurs in humans in which the psychological chronic stress component is already demonstrated, it is now also reported from the “psychomediation” perspective.

Skin scar diseases cannot be understood merely as esthetic complaints. They are associated with a variety of physiological reactions that can be modulated by many events, such as psychological ones. It begins with understanding about the interconnection between the skin and the central nervous system at an embryonic level. Their common origin is the ectoderm. Thus, depending on the reference, it can be said that the skin would be the external surface of the brain, or the brain would be the skin’s deepest layer.¹

Some skin diseases such as psoriasis,² atopic dermatitis,³ seborrheic dermatitis,⁴ herpes simplex,⁵ vitiligo,^{6,7} acne,⁸ alopecia,⁹ and urticaria¹⁰ are already included in the “psychophysiological disorders” category.¹¹ Keloid and hypertrophic scars should also be included in this category because of the impact of psychoemotional stress in their clinical features. The trigger, the maintenance, and/or the worsening of the signs

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and symptoms of these skin scar diseases are closely related to a stressful event (internal/psychological and/or external/environmental)¹² that activates neuroimmune–endocrine circuits.¹³

In this context, this review aims to open up new fronts for the comprehension of this pathological scar, looking for a better understanding of the patient as a whole in a psychoneuroimmune–endocrine way.^{14,15}

Psychoneuroimmune–endocrine systems and the skin

The skin has several elements of the nervous,¹⁶ immune,¹⁷ and endocrine systems.¹⁸ Some examples are corticotropin-releasing hormone (CRH) production by keratinocytes, melanocytes, and pilosebaceous units;¹⁹ adrenocorticotropic hormone (ACTH) and α -melanocyte-stimulating hormone (α -MSH) by keratinocytes, melanocytes, pilosebaceous units, fibroblasts, and endothelial cells;²⁰ and cortisol by keratinocytes and pilosebaceous units, among other hormones.²¹ Cytokines and growth factors such as interleukin 1 (IL-1) are also synthesized by keratinocytes, melanocytes, fibroblasts, and endothelial cells; IL-6 by the keratinocytes, fibroblasts, pilosebaceous units, and endothelial cells; tumor necrosis factor- α (TNF- α) by keratinocytes and melanocytes;^{22,23} and interferon- γ by keratinocytes and fibroblasts, among other elements of character, mostly proinflammatory. Therefore, the skin has a power plant of its own, with the capacity to produce locally all these factors related to other systems, speaking a common biochemical language and communicating via a complete bidirectional circuit involving shared ligands.²⁴ In addition to this local and bidirectional communication among systems, there is also a central–peripheral communication (Figure 1).²⁵

In this review, regulatory events of the skin homeostasis will be studied under the prism of psychogenic stimuli.²⁶ Besides the 5-hydroxytryptamine, acetylcholine, and inflammatory cytokines, signaling from areas of the limbic system (hippocampus, amygdale, and medial prefrontal cortex)²⁷ is able to release CRH from the hypothalamus paraventricular nuclei (Figure 2A). Adding to its classical performance in the pituitary gland, releasing ACTH, which acts on the adrenal glands cortex, providing cortisol, the CHR also elicits sympathetic responses in the locus coeruleus of the brain stem, releasing norepinephrine by peripheral nerve endings, and norepinephrine and epinephrine by the adrenal glands medulla (Figure 2B). The activation of the sympathetic nervous system also enables the production of other substances, including the catecholamines.

Nervous system

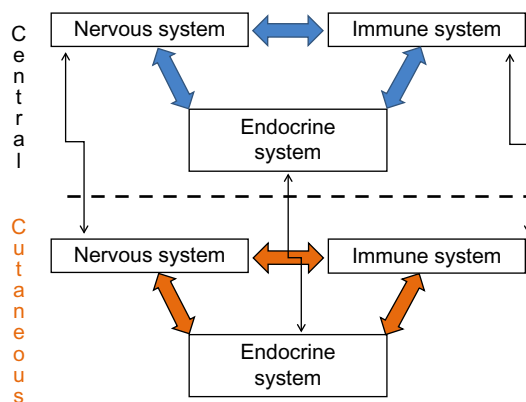


Figure 1 Integration of central and cutaneous neuro immune–endocrine systems.

The skin is able to express CRH as its receptors (CRH-R). The CRH-R1 α isoform is the predominant CRH receptor in the skin, and it is expressed in all major cell populations of epidermis, dermis, and subcutaneous tissue. By contrast, CRH-R2 is expressed predominantly in hair follicles, sebaceous and eccrine glands, and muscle and blood vessels.²⁸ In addition to CRH, the skin also expresses urocortin I and urocortin II messenger ribonucleic acid.²⁸ CRH-R1 binds to urocortin I but not to urocortin II, while CRH-R2 binds to urocortin II but not to urocortin I,^{29,30} leading to the belief that the skin has a depth of responsiveness and interaction to the environment that is little understood. Finally, skin produces the precursor protein proopiomelanocortin protein (POMC) and POMC-derived peptides that give rise to ACTH and other polypeptide products.^{19,31} Keloid fibroblasts express POMC.³²

Ito et al³³ have shown that human hair follicles can synthesize cortisol, and its synthesis is regulated by endogenous feedback controls. Thus, the skin apparently has a peripheral equivalent to the hypothalamic–pituitary–adrenal (HPA) axis that is fully functional. The peripheral skin HPA axis may coordinate or fine-tune peripheral stress responses with the central HPA axis. In addition to expressing components of the HPA axis, the skin also produces a number of other neuroendocrine signals, including prolactin,^{34–36} melatonin,³⁷ and catecholamines.³⁸

Besides the HPA axis, the skin is highly innervated with sensory nerves that produce neurotrophins and neuropeptides. Sensory nerves derive from the dorsal root ganglion in the skin, and C-fibers form the cutaneous sensory nervous system. Psychological stress leads to increased concentrations of cutaneous nerve growth factor (NGF).³⁹ NGF has a

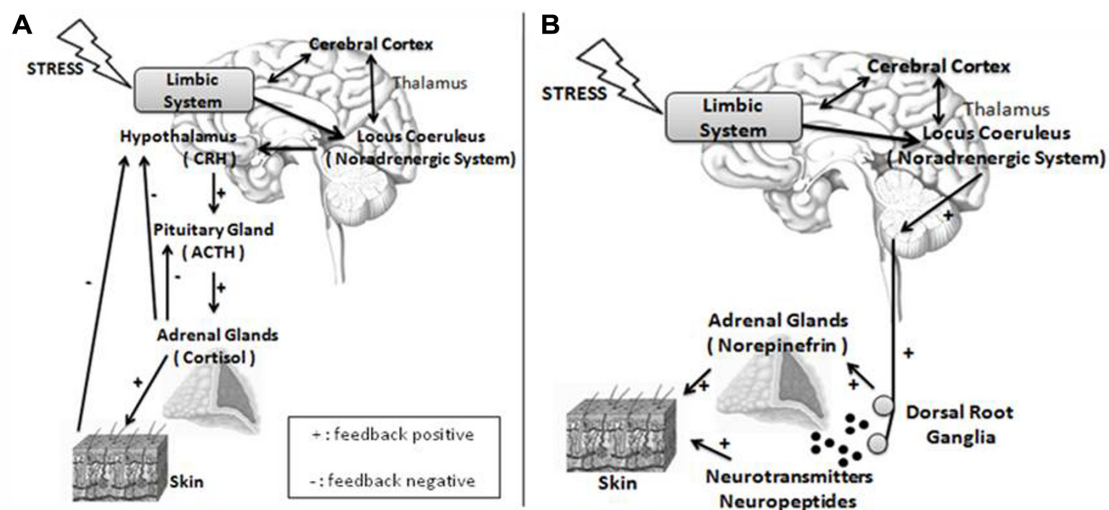


Figure 2 Nervous and endocrine pathways under stress.

Notes: The limbic system under stress: endocrine and nervous pathways to the skin. (A) Stress stimulating the hypothalamus–pituitary–adrenal axis. (B) Stress stimulating the sympathetic–adrenal–medullary axis.

Abbreviations: CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone.

number of biological activities, including 1) axon sprouting of peptidergic and sympathetic neurons; 2) promoting cross-talk between neural cells, glia, and immune cells; and 3) facilitating monocyte/macrophage migration through vascular endothelium.⁴⁰ NGF upregulates substance P (SP) nerve fibers in the dermis of stressed mice. Calcitonin gene-related peptide (CGRP), a potent vasodilator, is also upregulated in response to NGF.³⁹ SP and CGRP have different distributions within the skin, with SP nerve fibers detected in the dermis and subcutis, and CGRP nerve fibers are in the epidermis around the distal hair follicle and the arrector pili muscle.⁴¹

From this evidence, there is no way to understand skin diseases and their symptoms decoupled from psychological aspects. Clinical and experimental data support the assertion that the minds can start, stop, and influence biological events in the skin.⁴²

Psychoneuroimmune–endocrine system and keloid

At the moment of the loss of skin integrity

Considering the three super-systems, the nervous system is the one that responds more rapidly to noxious stimuli in the skin, due to its electrical nature. After a skin wound (endogenous origin such as acne, or exogenous such as a surgical incision or a mosquito bite), the loss of cutaneous integrity generates a “short circuit” in the skin battery, changing the outer skin pole to positive; this is responsible for generating an electrical current at the site of injury and initiating eletrotaxia. This current remains present until the

skin regains its integrity by wound healing, restoring its natural negative polarization. This current of injury helps eletrotaxia (primarily neutrophils and monocytes) initiate tissue repair (for better understanding of these definitions, see Hochman et al⁴³).

At the same time as the nerve endings directly influence the bioelectrical condition, they also lead afferences to the dorsal root ganglion, reporting the cutaneous status. Some of these stimuli reach the cerebral cortex. The efferent response is the neuropeptides and neurotransmitters release. The neuroelectric and neuropeptidergic components of the healing are inseparable parts of the neurogenic inflammation. The neurogenic inflammation level dictates the intensity of the subsequent phases of the healing.

Akaishi et al⁴⁴ proposed a neurogenic inflammation hypothesis for keloid formation. Other authors have also followed this perspective.^{45–47} However, all of them have analyzed just the peripheral and local nature of the lesion as a result of stressful stimuli (skin stretch and mechanotransduction). Considering the existence of central–peripheral ways of communication between the central and the cutaneous nervous system, it is possible to extrapolate the opposite route, based on the same grounds, in which central nervous stimuli would trigger a similar response in the skin. The neurogenic inflammation level of the healing process is directly related to the amount and the functionality of cutaneous nerve fibers. Kadanoff⁴⁸ was the pioneer in demonstrating the relationship of innervation with keloid. Hochman et al⁴⁹ showed higher density and depth of nerve fibers in the keloid than the skin. A higher density of nerve fibers was also demonstrated in

hypertrophic scars when compared to normal scars.^{50–52} In turn, the lower density of nerve fibers in the keloid epidermis could be related to chronic stimulation of conductive nerve endings of itching, similar to the fibers of the nociceptive stimuli, and it would be an autoregulatory mechanism for modulation of intensity and persistence of sensory inputs.⁵³ In this context, botulinum toxin has recently come to prominence as a form of treatment.^{54–57} For the future, capsaicin, the functional denervator, may also appear as an alternative.⁵⁸

Before the loss of skin integrity

The basal skin condition is a very important factor in healing disorders. The cutaneous inflammatory status is influenced, among other factors, by ultraviolet radiation,^{12,59} feeding,^{60–62} obesity and metabolic syndrome, and stress of psychological origin.⁶³ This could explain the bizarre temporal character of keloid, in that an individual can develop it in different periods of their life.⁶⁴ Black skin absorbs more ultraviolet radiation than the other skin color types. This is a disadvantage because the more radiation absorbed, the more skin inflammation, increasing this important risk factor which corresponds to a higher prevalence of keloids in this population.

The immune response and the immune system can be modulated by the interactions between essential fatty acids, eicosanoids, and free radicals coming from the diet. For the essential fatty acids, if there are enhanced arachidonic acid levels plus deficiency of precursors (linoleic acid, g-linolenic acid, and dihomo-g-linolenic acid) and some inflammatory competitors (dihomo-g-linolenic acid and eicosapentaenoic acid), it will result in an inevitable overproduction of proinflammatory metabolites, which enhances a pathologic inflammation, both systemic and local, in the skin. This scenario is seen in patients with keloid.⁶⁵

Psychological stress can amplify both the bioelectric and neuropeptidic components of the neurogenic phase of the healing inflammation. Sweat and sebaceous secretion as a result of emotional factors^{66,67} increase the electrical conductivity of the deeper layers and the impedance of the stratum corneum, respectively, increasing the current of injury and the eletrotaxia at the moment of injury. On the other hand, the stress chronically stimulates the neuroimmune–endocrine circuit and the sensory system.^{68–70} The binding of neurotransmitters, neuropeptides, and neurohormones (acetylcholine, CGRP, substance P, CRH) in the mast cells receptors makes them degranulate. From the degranulation, several proinflammatory mediators such as IL-1, IL-6, growth factors (NGF, vascular endothelial growth factor [VEGF], transforming growth factor- β [TGF- β]), TNF- α , and histamine are

released and refeed the cycle, creating a chronic inflammatory condition.¹² The intimate relationship and interaction between mast cells and myofibroblasts support the important role of mast cells and their mediators in the pathogenesis of the keloid.^{71,72} TGF- β ,^{73–76} VEGF,⁷⁴ histamine,⁷⁷ TNF- α ,⁷⁸ and IL-6^{79–81} have already been implicated in the pathogenesis and symptomatology of the keloid.⁸²

In summary, stressed patients exacerbate the neuroimmune–endocrine system, and that causes basal inflammatory metabolic activity on the individual skin, which enhances the neurogenic inflammation phase during the healing process. In other words, people bring on the inflammation themselves when their “nerves are on edge”.⁴³

Furtado et al⁸³ were the first to show a direct correlation between stress and keloid. Patients with fibroproliferative scars who were candidates for surgical resection and postoperative radiotherapy underwent evaluation of psychological stress on the day before the surgery. The parameters evaluated were pain and itching, quality of life, perceived stress, depression and anxiety – through questionnaires and scales – salivary cortisol, and minimum and maximum galvanic skin response (GSR) at rest and under stress (when filling in questionnaires). The patients were evaluated postoperatively at 3, 6, 9, and 12 months. Each time the patients returned to the medical service, two specialists classified the lesions in nonrelapsed and relapsed patients. The relapsed group presented higher values in GSR during the stress situation. The chance of relapse increased 34% for each increase of 1,000 arbitrary units, at maximum GSR in stress. Thus, psychological stress increases the chance of relapse in postoperative keloid.

Final considerations

Keloid management is still considered a challenge for physicians and researchers. This is a healing benign neoplasm exclusive to humans whose therapeutic modalities are unsatisfactory and present a high rate of recurrence.^{84,85} Several hypotheses regarding its physiopathogenesis have been postulated.^{44,86–89} Currently, a genetic cause has received the greater prominence, with a large number of publications about it.^{90–92}

However, it must be understood that genetic and environmental influences are interconnected in a complex way. Currently, a widely accepted model is the stress–diathesis model, according to which stressful situations (the precipitating factor) will affect people in different ways due to inherited vulnerabilities (a predisposing factor). Moreover, according to this model, a genetic predisposition to disease development (“diathesis”) may remain latent until stress

events, which can be represented by psychosocial factors interacting with biological characteristics of a person, make the disease unfold.⁴²

Environmental factors are certainly critical in defining phenotypes during early development, and they continue to influence phenotypes throughout the life cycle of an organism. Nearly every aspect of development and behavior is affected by both personal experience, that is gained through the environment, and the genetic makeup. Environmental factors can affect and alter gene expression, while genes can define how people respond to different environments. Indeed, it is actually superficial to debate whether nature or nurture is more important. In truth, the relationship between genetic determinants and the environment is so completely entwined that you cannot look at an individual and judge which contribution is more valuable. Together, the continual interplay of both genes and ever-changing environmental factors determines who people are.

Keloid and hypertrophic scars are different phenotypic expressions of the same phenomenon and can exemplify the complexity of the disorder.⁹² It is certain that the treatment of these healing disorders cannot focus on one single aspect. It is necessary to understand the wide spectrum of communication between the three super-systems. The release of hormones, neural transmitters, substances, and immune cells creates an inflammatory environment that stimulates the fibrogenesis (the expression of proinflammatory genes are inserted in this context).^{89,93–95} On the other hand, personality and coping styles reflect individual differences in appraisal and response to stressors that may influence neuroimmune–endocrine functions.

Thus, skin disorders should be interpreted in a holistic way; in other words, a good practice evaluates the individual as a whole, under a psychoneuroimmune–endocrine functional perspective. Since most, or perhaps all, cases of cutaneous somatization have been long neglected, they now become the target of research in which the psychogenic part has gained prominence, because there is no dermatosis in which the psychological factor is not involved.⁴³ The trigger to wound healing depends on neurogenic factors (electrical and neurosecretory) which, in turn, are premodulated by psychological aspects and adjusted by immune and endocrine factors. Any change in these circuits may interfere in the normal formation of a scar, resulting in wound healing deficit (atrophic scars and ulcerations) until hyperproliferative healing (hypertrophic scars and keloid).

Based on these principles, the treatment of patients with keloid should be conducted by a multidisciplinary team. The

joint and integrated approach of physicians, psychologists, nurses, nutritionists, and physical therapists knowledgeable of its psychoneuroimmune–endocrine etiology may be able to provide relief to those who suffer from a deformative, stigmatizing disease that is still without a cure.

Acknowledgment

Tribute is paid to the great master Professor Bernardo Hochman. This is a posthumous tribute to him, he devoted much of his life to studying, understanding, teaching, and disseminating what the keloid really is. We will remember forever his words “If the eyes are the mirror of the soul, the skin is the mirror of the mind.”

Disclosure

The authors report no conflicts of interest in this work.

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