Review Article

Brain–Skin Connection: The Contemporary Perspective through Neuroendocrinology

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Abstract

This review summarizes the novel and precious data on the direct effects of ancient neuroendocrinologic molecules on the skin and hair and additionally the active production of these hormones by resident skin cells. The data are extracted from PubMed using the keywords neuroendocrinology, hormones, skin, hair follicle, pituitary, hypothalamus, thyroid, and prolactin. The most important neuroendocrinologic axis is composed of corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol (CRH–ACTH–cortisol) and is related to stress. The CRH–ACTH–cortisol axis is demonstrated to be fully functional in the skin. This review furthermore points out to a possible neuroendocrinologic mechanism likely to explain the association between psychological stress and skin and hair diseases.

Keywords: Hair follicle, hormones, neuroendocrinology, skin

Introduction

The skin serves as a barrier isolating the organism from the external environment. Besides the mechanic protective function, a wide range of different functions are established and increasingly recognized. Even recently, epidermis is proposed to be the third brain after the accepted opinion on the digestive system as the second brain of the body.[1] Skin is not only the primary end organ for environmental stimulators but also produces various hormones and neuromediators.

In this review, we briefly focused on the intimate relationship between brain activities such as reception and processing of external information and skin reactions including immune, endocrine, and inflammatory responses.

The Arousal of Skin Neuroendocrinology

The connection between the skin and the brain is recognized even in the prehistorical times as the aggravation of many dermatological diseases by psychological stress. Furthermore, the alterations of quality of life and mood disorders are commonly observed and defined by clinicians throughout the dermatological practice. The elevated levels of inflammatory molecules such as cytokines, neuromediators, and neurotrophins due to skin diseases such as psoriasis, atopic dermatitis, and hidradenitis suppurativa were also hypothesized to be the cause of psychiatric comorbidities in dermatological patients.[2,3]

The skin can serve both affective and effective properties attending crucial functions through the intertalk between the body and the external environment.

As an ordinary sensory organ, the skin collects the signals from the environment in an appropriate way and as an exceptional finding can process these data and react to stressful events independent from the nervous system. In other words, the skin, itself, has the potential either to initiate an emotional response to the changing environmental conditions or evoke adaptive physiological responses by the contribution of keratinocyte-derived molecules. The neuroendocrine system begins to work out from the beginning in the reception step by the regulation of the intensity of environmental signals – the

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differentiation of environmental noise from appropriate signals – and only can be activated upon receiving signals above the activation threshold levels. The environmental signals clearly induce significant alterations of the immune and pigmentary systems of the skin. Thus, these systems were once accepted as fundamental independent responders to different types of stress. The skin neuroendocrine system is found to serve important implications on these abovementioned systems also with a potential to enter the systemic circulation and cause systemic effects.[1]

The skin has various receptors for neuronal and endocrine ligands, but its active production of hormones and neurotransmitters is an outstanding discovery and the cause for increased attention on neuroendocrinology.

The acquired data changed the position of the skin from a passive player in whole-body homeostasis to an active one.

Developmental Biology of the Skin: An Emphasis on Shared Origin with the Nervous System

Epidermis and dermis substantially derive from different embryonal layers as the ectoderm and mesoderm, respectively. Adnexal structures arising from the precise mesenchymal–epithelial interactions are also ectoderm derived. The central and peripheral nervous system, retina, and medulla of the adrenal gland derive from the ectoderm, making an intimate connection, in other words, a common molecular syntax reasonable for the epidermis and adnexa with these structures.

Keratinocytes, the complete structure of the hair follicle including the sebaceous and apocrine glands and also eccrine sweat glands, derive from the ectoderm-originated embryonal outer epithelium.

Similarly, the anterior lobe of hypophysis derive from the outer epithelium.[4] This common ancestral relationship with the anterior hypophysis gland is noteworthy, as growing evidence indicates the existence of identical hypothalamic–pituitary–end organ axes in the skin with relevant feedback mechanisms.

Fundamental Concepts in Skin Neuroendocrinology

General neuroendocrinology describes several central axes through which the brain controls the endocrine glands. Prior to the introduction of these well-known molecules with unfamiliar properties related to the skin, these principles should be kept in mind:

The skin itself can express these molecules and include their receptors in the adjacent layers in the apparent absence of strict compartmentalization as observed in the pituitary gland.

Current evidence suggests that drugs, the skin microbiome, and physical stimulants such as ultraviolet radiation, oxidative stress, and also psycho-emotional stress may directly interact with the intracutaneous production of hormones and neuromediators.[5]

Even both epidermal and hair follicle keratinocytes express hormones, neuromediators, and neurotrophins; the regulation and effects of these molecules are distinct for hair follicle and epidermal cells. For example, thyrotropin-releasing hormone (TRH) is shown to serve significant melanogenic stimulation in the hair follicle, which did not appear to be alike in the epidermal cells. Through the contribution of hair follicle organ cultures without the need for animal studies, the science of skin neuroendocrinology is preferentially evolving in the hair follicle.[6] Peripheral nerves in the skin influence skin function through secreted neuroinflammatory molecules.

Neuroendocrine axes pose critical regulatory roles for the hair cycle. The characteristic distribution of androgen-sensitive and androgen-resistant hair follicles in different genders is responsible for the typical phenotype of androgenetic alopecia, which is also valid for different hormones. A typical example is the differential effect of prolactin on the hair cycle; while it promotes occipital catagen hair in males, it stimulates hair growth in female frontotemporal hair follicles.[6]

Many hormones also work as a cytokine or a neuromodulator. Thus, the distinctions between hormones, neuropeptides, neurotransmitters, and cytokines are less clear.

A lot of broad questions cover up the field as to what extent the skin equivalents communicate with or depend on their central neuroendocrinologic axes.

Regarding the huge amount of cell number including epidermal and hair follicle cells, Paus *et al*. suggested that even the production of hormones was defined at a minimal level, there might still be a theoretical risk of contributing to systemic neurohormone levels, which had to be investigated further.[6]

Hypothalamus–Pituitary–End Organ Axis with Corresponding Skin Equivalents

The skin includes a full-functional hypothalamus–pituitary–adrenal axis (HPA), and the hypothalamus–pituitary–thyroid (HPT) axis of the skin is regarded as a partial equivalent of the central counterpart.[7,8] Despite the absence of an end organ, due to the structural integrity with HPT axis through its central control by TRH, the evidence on the functions of prolactin related to the skin will also be discussed in this context.

Hypothalamus–pituitary–adrenal axis

Upon exposure to stress, hypothalamic neurons secrete some hormones. HPA involves subsequent upregulation of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol [Figure 1]. Following the discoveries on the expression of different elements belonging to HPA axis in the skin, the fully functional peripheral equivalent of HPA axis is first demonstrated in 2005 in microdissected, organ-cultured scalp hair follicles.[9,10] CRH induces the secretion of proopiomelanocortin-derived neuropeptides

such as alpha-melanocyte-stimulating hormone (α-MSH), β-endorphin, and ACTH in the pituitary gland. In addition to the roles of CRH, ACTH, and cortisol, α-MSH and β-endorphin have distinct functions in the skin [Figure 2].

CRH attends a wide range of actions in the skin including both proliferative and anti-proliferative or inflammatory and non-inflammatory features depending on the resident cell type. CRH is produced by epidermal and hair follicle keratinocytes, mast cells, and melanocytes. The skin involves two types of CRH receptors such as CRH-R1 and CRH-R2. The expression of CRH-R1 is widespread in epidermis, dermis, and subcutaneous tissue, whereas CRH-2 is only expressed in hair follicle keratinocytes and papillary fibroblasts.[11]

As a downstream molecule of HPA pathway, ACTH reaches to the adrenal cortex's outer layer and exerts pro-inflammatory features and stimulates corticosteroid production through melanocortin-2-receptor. ACTH mainly induces the production of cortisol in the surreal cortex as a stress hormone and concurrently stimulates a pro-inflammatory cytokine, interleukin-18 in epidermal keratinocytes as a T-cell activator.

This axis is unique in skin neuroendocrinology due to three different aspects. First, the most prominent neurohormonal response to psychological stress occurs through HPA axis; thus, this axis embraces important issues mainly including the connection of skin diseases and stress. Second, the skin HPA axis has profound suppressive implications on the immune system, mainly described as the suppression of Th1-mediated immunity with a shift toward Th2-mediated humoral immunity, admixing the effects of neuroendocrinology with skin immunology. The third perspective includes as a very commonly used drug in dermatological practice, topical corticosteroids may impact the intrafollicular HPA axis equivalent.

Hypothalamus–pituitary–thyroid axis

Recently, the discoveries on the HPT axis equivalent of the skin pointed out to exciting different roles of this axis that could be translated to general neuroendocrinology.

Slominski *et al*. first described the expression of members belonging to this axis including TRH, thyroid-stimulating hormone (TSH) and thyroid hormones (T3 and T4), and the receptor transcripts of TRH and TSH.[12]

The established functions of HPT axis hormones are summarized in Table 1.

Table 1: The functions of hormones belonging to the hypothalamus-pituitary-thyroid axis equivalent of the skin

Hormone	Effects on the skin and the hair follicle
TRH	Effects on epidermal hormone expression
	Stimulation of epidermal TSH expression
	Regulation of intracutaneous prolactin expression
	Stimulation of hair pigmentation
	Intrafollicular melanin synthesis
	Tyrosinase gene expression and activity
	Dendrite formation by hair follicle melanocytes
	Increased melanosome transfer to keratinocytes
	Possibly occurs through upregulation of MITF
	Keratinocyte mitochondrial function
	Enhanced mitochondrial activity and biogenesis
	Regulation of keratin expression
	Hair keratins
	Stem cell keratins (K15, K19)
	Effects on the hair cycle
	Anagen promotion
TSH	Keratinocyte mitochondrial function
	Enhanced mitochondrial activity and biogenesis
	Regulation of keratin expression
	Hair keratins
	Stem cell keratins (K15, K19)
T3, T4 (generated mainly outside the skin)	Regulation of keratin expression
	Effects on hair cycle
	Anagen promotion
	Improved wound healing
	Regulation of epidermal stem cell functions

TRH: Thyrotropin-releasing hormone, TSH: Thyroid-stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, MITF: Microphthalmia-associated transcription factor

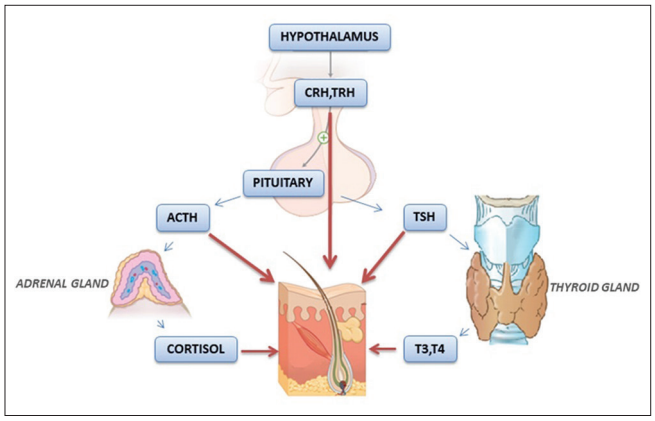

Figure 1: The schematic representation of the hypothalamic–pituitary–thyroid and hypothalamic–pituitary–adrenal axes with established effects on the skin

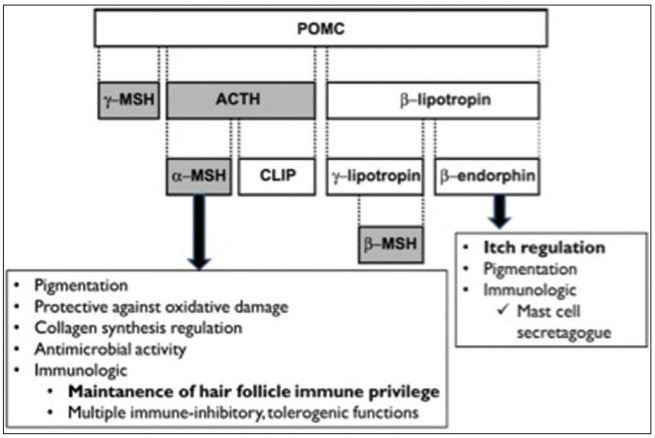

Figure 2: Proopiomelanocortin-derived hormones with their relevant functions on the skin and hair follicle

The novel function of TRH on melanocytes as a strong melanogenic agent is demonstrated in hair follicle organ cultures, but this effect was not replicated for epidermal cells.[13] These findings together can be translated to the clinical setting as the selective effect on hair follicle pigmentation points out to a possible therapeutic role to prevent or even reverse existent hair graying.

The effects of TRH and TSH on keratinocyte mitochondrial functions were detected in both epidermis and hair follicle keratinocytes.[7,8] These results gave the first hints about the regulatory role of neuroendocrinology on mitochondrial functions and served as a research frontier for the possible role of TRH/TSH in other tissues with high-energy demands. Starting from the mitochondrial theory of aging, the modulation of decreasing mitochondrial function in senescent hair follicles and other tissues by therapeutic strategies targeting TRH/TSH is suggested to be possible.[6]

An intensively searched function of HPT axis related to the skin includes the control of keratin gene and protein expression in human epidermis and hair follicle.[14] Keratins attend a wide range of regulatory functions for epithelial cell proliferation, differentiation, migration, apoptosis, wound healing, carcinogenesis, and hair follicle cycling beyond their mechanical properties in order to form a scaffold for keratinocytes.[15] Triiodothyronine (T3) was the first of various hormones revealing a regulatory effect on keratin expression. Hypothyroid mice exhibit decreased K6 expression and the exposure of cultured keratinocytes to T3 resulted in increased gene expressions of K6, K16 and K17.[16] Subsequent studies, especially designed on human hair follicle cultures, reported the differential expression of keratin sets by different molecules including TRH/TSH, prolactin, CRH, endorphins, catecholamines, and parathyroid hormone-related peptide.[17-26] The effects of these hormones on keratin expression are not fully understood. For example, in the human hair follicles, despite the widespread presence of TRH immunoreactivity including the outer root sheath (ORS), the TRH-R immunoreactivity is confined to the inner root sheath. Nevertheless, TRH strongly regulates the expression of keratins in ORS such as keratin.[6,14,17]

The regulation of stem cell-associated keratins is especially reported with prolactin and TRH. However, the consequences of this affiliation and whether it could serve as a therapeutic strategy are unknown.[6]

Hypothalamic control of prolactin

The stimulating effects of TRH on prolactin were reported both in general and skin neuroendocrinology.[27,28] Prolactin is reported to be involved in hair cycle and sebum production and also as discussed previously in HPT axis attend regulatory roles in keratin expression.

The function of prolactin on hair cycle is gender and species specific and is a typical example demonstrating why the data derived from animal studies should not be generalized to human situations. Prolactin is found to promote catagen in mouse hair follicles.[29] The promotion of occipital catagen hair in males and conversely stimulation of hair growth in frontotemporal hair follicles in females were reported in human studies.[30]

Neuroendocrine Stress Response Systems in Human Skin

The relationship between dermatological diseases and psycho-emotional stress was explained through the psychoanalytical perspective and also immunological measures such as cytokine levels. Exposure to sound, restraint, and foot-shock stress caused remarkable perifollicular neurogenic inflammation and suppressed hair growth in mouse studies, suggesting a possible explanation for stress-induced hair loss.

The detection of increased nerve–mast cell contacts in inflammatory skin diseases such as psoriasis and atopic dermatitis is a starting point for the adaption of skin neuroendocrinology into this model, designated by the phrase of "stress-induced neurogenic skin inflammation."

Stress-induced neurogenic inflammation gathers neuroendocrinology and neuro-immunology together in order to contribute to the pathogenesis of many skin diseases and reveals skin mast cells as the central player leading to a vicious cycle of inflammatory events upon activation. The activation and degranulation of mast cells occur upon increased levels of mediators including CRH, ACTH, nerve growth factor, and substance P.

Conversely, endogenous and exogenous agonists of cannabinoid receptor 1 (CB-1) suppress both the maturation and degranulation of mast cells and hold promise as a therapeutic approach for the epidemic of allergic diseases related to the skin, lungs, and upper respiratory airway. The endocannabinoid system involves three main parts including the endogenous ligands such as anandamide and 2-arachidonoylglycerol, the enzymes responsible for the synthesis and metabolism of these products, and the receptors such as CB-1 and CB-2. Tonic CB-1 signaling is essential for the prevention of excessive mast cell activation and degranulation.

The involvement of sympathetic–adrenal–medullary axes to the systemic stress response is also appreciated, and the skin also involves a peripheral catecholamine system equivalent. Originally, the role of catecholaminergic signaling pathway in dermatologic diseases relies on the long line of research demonstrating the role of β-adrenergic signaling in atopic eczema about five decades ago.[31] Apart from the appreciated production of catecholamines from skin nerve endings, epinephrine is also synthesized by keratinocytes and additionally adrenergic receptors are expressed in epidermal keratinocytes and melanocytes.[32] The activation of β-2 adrenergic signaling in keratinocytes with epinephrine induces the production of cyclic adenosine monophosphate though protein kinase C activation, and the result is increased calcium

concentration. Hence, calcium level has important regulatory functions on both epidermal proliferation and differentiation; catecholaminergic signaling is expected to influence epidermal health.[33] Dermal fibroblast functions including migration and collagen production are also demonstrated to be influenced by catecholaminergic signaling in the presence of beta-adrenergic receptors, suggesting a possible mechanism for the detrimental effect of stress on wound healing.[34] Recently, the inhibition of adrenergic signaling with timolol is shown to result in improved healing in burn and radiation wounds.[35]

The brain is considered to be protected by the blood–brain barrier and assumed as a master of the organism collecting inputs and sending unidirectional commands throughout the body for decades. Recently, animal studies confirmed the clear effects of chronic systemic inflammation on the brain by neuroimaging findings. The brain inflammation is somehow triggered by chronic inflammatory diseases. There is an open field for the investigation of the possible effects of chronic skin inflammation on brain inflammation and functioning, and researches are likely to occupy the arena in dermatology in the near future. The interaction between skin and general neuroendocrinology might be a mechanism for such an association.

Conclusion

Neuroendocrinologic molecules may represent more biological activities than their conventional features, including the effects on epithelial and mesenchymal growth and regeneration, possibly related to wound healing and tissue homeostasis. In future, the cumulative data on these ancestral functions may serve as a therapeutic tool and can be translated for targeted therapies in various dermatological disorders.

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Conflicts of interest

There are no conflicts of interest.

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