Published in final edited form as:
Expert Rev Dermatol. 2013 ; 8(6): 581–583. doi:10.1586/17469872.2013.856690.

Neuro-immune-endocrine functions of the skin: an overview

Reza Nejati[‡],
Department of Pathology and Laboratory Medicine, University of Tennessee Health Science Center, 930 Madison Avenue, 5th Floor, Memphis, TN, USA

Diane Kovacic[‡], and
Department of Pathology and Laboratory Medicine, University of Tennessee Health Science Center, 930 Madison Avenue, 5th Floor, Memphis, TN, USA

Andrzej Slominski
Department of Pathology and Laboratory Medicine, University of Tennessee Health Science Center, 930 Madison Avenue, 5th Floor, Memphis, TN, USA and Department of Medicine, Center for Adult Cancer Research, University of Tennessee Health Science Center, Memphis, TN, USA, Tel.: +1 901 448 3741, Fax: +1 901 448 6979

Andrzej Slominski: aslomins@uthsc.edu

Keywords

cannabinoids; CRH; HPA axis; HPT axis; melatonin; opioids; POMC; serotonin; vitamin D

For many years, skin was just thought of as a barrier to protect against a variety of insults from the external environment. Our body's largest organ is gradually revealing itself to be a complex organ involved in multiple neuro-immuno-endocrine functions [1,2]. Skin functionally consists of two compartments: the epidermis with keratinocytes, melanocytes and Langerhans cells and the dermis composed of fibroblasts/fibrocytes, nerve endings, vasculature and immune cells. It has been shown that the skin, with its various components, has the ability to communicate and regulate itself through the production of various cytokines, neurotransmitters, neuroendocrine hormones and their corresponding receptors. These neuro-immuno-endocrine functions are tightly networked to central regulatory systems [1]. Considering the fact that the skin is the front-line barrier of external stressors, such as solar radiation and bacteria, it seems logical that the skin has developed an effective sensory and signaling system to differentially react to changes in the external environment. These capabilities allow it to protect, restore and maintain the local and global homeostasis that is crucial for survival [2]. The skin complexity would be surprising if we did not remember that its embryologic ectodermal-derived sibling is the brain. We will briefly discus some of these axes here.

[‡]Authors contributed equally

Financial & competing interests disclosure
The research described and writing of this commentary was supported by grants R01AR052190, 2R01AR052190-06A1 and 1R01AR056666-01-A2 from the NIH/NAIMS and IOS-0918934 from the NSF to ATS, and by the dermatopathology fellowship (DK) and residency in pathology (RN) at the UTHSC. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

Equivalent of hypothalamo–pituitary–adrenal axis in the skin

More than 15 years ago, the concept of a cutaneous equivalent of the hypothalamo–pituitary–adrenal (HPA) axis was proposed [3]. It was suggested that skin expresses a homolog of the HPA axis to regulate local stress responses [3]. Studies from the last two decades have shown definitive evidence that skin, in response to a variety of stressors, is capable of producing many of the hormonal elements expressed in a systemic responses to environmental stressors, that is, corticotropin releasing factor/hormone (CRF), proopiomelanocortin (POMC)-derived β-endorphin (β-END), adrenocorticotropin (ACTH) and α-melanocyte-stimulating hormone (α-MSH), the corresponding CRF-receptor 1 (CRF1) melanocortin and opiate receptors [4,5]. Also, it has been shown that the key enzymes of corticosteroid synthesis that results in the cutaneous production of corticosterone and cortisol are expressed in the skin (reviewed in [2]). In addition, depending on the type of stressor and its intensity, the skin can activate systemic HPA either by neural signaling via afferent nerve fibers to the brain or by skin-derived factors that may activate pituitary gland or adrenal cortex [2,5]. This cutaneous equivalent of the central HPA axis is nonrandom and models the same hierarchical, organizational and cell type-specific regulatory loops structure.

Cutaneous opioid system

Endogenous opioid peptides are largely derived from two different precursor proteins. The first is POMC, which is the precursor for ACTH and endorphins, mainly β-END. Second, proenkephalin that is transformed into multiple enkephalins, predominantly Leu-enkephalin and Metenkephalin [4,6]. The POMC gene and protein and POMC-derived peptides (ACTH, α-MSH and β-END) have been detected in epidermis, dermis and adnexa. Tanning lovers may be interested to note that UV-induced production of cutaneous β-END [7] resulting from local transcription, translation and further cleavage of POMC may play a role in addiction to UV despite its negative consequences [1].

Cutaneous cannabinoid system

At least two cannabinoids receptors, CB1 and CB2, have been discovered in the skin. These receptors play an important role in the abundant neuroendocrine activities of the skin. Endocannabinoid system (ECS) participates in a number of pathophysiological processes in the skin via these receptors, such as profound anti-inflammatory, antipruritic, antitumorigenic and antinociceptive effects. Additionally, it has been shown that various skin tumors (e.g., basal and/or squamous cell carcinoma) express both CB1 and CB2 receptors [8]. Some studies have shown that the administration of synthetic CB1 and CB2 agonists could inhibit the growth of some malignant skin tumors [8]. ECS also inhibited in vivo growth of mouse melanomas that expressed CB1 and CB2 by decreasing growth, proliferation, angiogenesis and metastasis formation, while increasing apoptosis [8].

Cutaneous cholinergic system

Communication between the cutaneous neuroendocrine system and the rest of the body is partly achieved via the cholinergic system. The cholinergic system plays a key role in the regulation of keratinocytes' homeostasis [9]. Acetylcholine modifies keratinocyte differentiation, adhesion, motility and cell cycle. The cholinergic system is also implicated in skin diseases such as psoriasis, palmoplantar keratoderma (Mal de Meleda type), atopic dermatitis, vitiligo and pemphigus.

Serotoninergic & melatoninergic systems in the skin

The hydroxylation of L-tryptophan via tryptophan hydroxylase occurs in the skin, which is the rate limiting step in the formation of serotonin, melatonin, serotonin and *N*-acetylserotonin (reviewed in [10]). Unlike the pineal gland that is separated from the external environment and produces melatonin based on circadian rhythm, skin can produce this hormone as needed in response to its environment. Some of the effects are of melatonin that are mediated from direct, receptor-independent effects, acting as a powerful free radical scavenging molecule. It also functions to modify hair growth cycling and works to maintain mitochondrial function that is necessary for cell homeostasis [10]. Local melatoninergic systems could also modify the activities of the cutaneous neuroendocrine network and affect global homeostasis.

Equivalent of hypothalamic–pituitary–thyroid axis

The skin can also communicate with itself and systemically via both the thyroid-releasing hormone and thyroid-stimulating hormone (TSH) receptors, which are expression in various skin cell types including melanocytes, keratinocytes, fibroblasts and hair follicles [11,12,13]. The effects of thyroid diseases on skin have been known for decades, but the possible mechanisms were unclear. The discovery of these receptors within the skin have led to the concept of a cutaneous hypothalamic–pituitary–thyroid (HPT) axis that would demonstrate similarities to and differences with the central HPT axis [13]. Of particular interest is the possible role of the exposure of TSH-R to immune cells in damaged keratinocytes or fibroblasts [13]. This pathological exposure can trigger either production of anti-TSH-R antibodies leading to the uncontrolled stimulation of the thyroid gland or generation of anti-TSH-R clones of T lymphocytes leading to immune destruction of the thyroid. These concepts, originally proposed by Slominski et al. have been recently re-emphasized defining a role of skin in thyroid autoimmune diseases [12].

Also it has been shown that T4 stimulates the proliferation of hair follicle keratinocytes and T3 inhibits their apoptosis [14]. In addition, it has been suggested that thyroid hormone receptors might suppress invasiveness and metastatic ability of skin tumors as shown in mouse knockout models (reviewed in [2]).

Cutaneous secosteroidogenic system

Vitamin D and its analogs belong to a group of hormones called secosteroids, which chemically resemble cholesterol. The biologically active secosteroid 1,25(OH)2D3 (calcitriol) is well known for its role in calcium and phosphorus regulation and also its role in keratinocyte differentiation. Calcitriol is sequentially synthesized, beginning in the skin with the synthesis of vitamin D3 from 7-dehydrocholesterol (pro-vitamin D3) via a nonenzymatic reaction triggered by UV light. Vitamin D3 is then further hydroxylated in the liver to 25(OH)2D3. In the kidney, 25(OH)2D3 undergoes additional hydroxylation at position C1 resulting in the biologically active calcitriol (reviewed in [7]). The sequential hydroxylation of vitamin D3 was also found to occur in the skin, resulting in locally produced calcitriol, which acts like a steroid when bound to its nuclear receptor, vitamin D receptor [17]. Topical therapeutic agents consisting of vitamin D derivatives are currently being used to treat psoriasis. However, one of the potential side effects of these derivatives is hypercalcemia.

Recent work investigating novel pathways of vitamin D3 metabolism via the steroidogenic cytochrome P450scc (CYP11A1) show that previously unrecognized vitamin D metabolites can be produced in the skin [15]. These novel derivatives are biologically active and do not result in hypercalcemia even if present at high doses. More importantly, these derivates

show anticancer, antiproliferative, anti-inflammatory and prodifferentiating effects which may be developed as therapeutic agents. The efficacy of using vitamin D as an anticancer treatment will also depend on the cytochromes P450 up- or downregulated in the local skin environment. Some vitamin D metabolizing cytochromes, such as CYP24A1 and CYP3A4, inactivate vitamin D and its derivatives (reviewed in [18]). Specific cytochrome inhibitors may need to be added in addition to vitamin D therapy in order for the treatment to be effective in patients with increased levels of these cytochromes (reviewed in [2]).

In addition to vitamin D production, human skin also expresses genes encoding enzymes involved in the sequential metabolism of cholesterol to pregnenolone and to corticosteroids [9]. Mammalian skin is an extra-adrenal site of mineralo/glucocorticoid synthesis, which is regulated by endogenous and environmental factors [2]. Skin is also an important site for estrogen and androgen production, activation and metabolism (reviewed in [19]). These molecules act in intra-, auto- or paracrine fashions to regulate local homeostasis. Furthermore, skin and its subcutaneous tissue constitute an important source of estrogens and androgens in females, especially after menopause.

Conclusion

The expanding list of neuroendocrine elements that are expressed in the skin supports a strong role for this system in cutaneous biology. These fascinating findings have raised many other questions. Could elements of these cutaneous neuro-immuno-endocrine axes be used as targets for therapy or immunoresponse? Can we use any of these elements as markers of survival and metastasis? Also, the recent studies in our lab have demonstrated different expression of HPA axis elements in genetically different murine skin [20]. These findings raised many more questions such as: are these genetic predetermined differences implicated in the progression of skin tumors or pigmentary disorders? Could any of these genetic differences potentially be a predictor of therapy response? We hope that future studies open a new window to the mysterious world of many skin diseases, as well as the development of targeted therapeutic treatments.

References

1. Slominskin A, Wortsman J. Neuroendocrinology of the skin. Endocr Rev. 2000; 21(5):457–487. [PubMed: 11041445]
2. Slominski AT, Zmijewski MA, Skobowiat C, Zbytek B, Slominski RM, Steketee JD. Sensing the environment: regulation of local and global homeostasis by the skin's neuroendocrine system. Adv Anat Embryol Cell Biol. 2012; 212:v, vii, 1–115. [PubMed: 22894052]
3. Slominski A, Mihm MC. Potential mechanism of skin response to stress. Int J Dermatol. 1996; 35(12):849–851. [PubMed: 8970839]
4. Slominski A, Wortsman J, Luger T, Paus R, Solomon S. Corticotropin releasing hormone and proopiomelanocortin involvement in the cutaneous response to stress. Physiol Rev. 2000; 80(3): 979–1020. [PubMed: 10893429]
5. Slominski AT, Zmijewski MA, Zbytek B, Tobin DJ, Theoharides TC, Rivier J. Key role of CRF in the skin stress response system. Endocr Rev. 2013 (Epub ahead of print). 10.1210/er.2012-1092
6. Slominski AT, Zmijewski MA, Zbytek B, et al. Regulated proenkephalin expression in human skin and cultured skin cells. J Invest Dermatol. 2011; 131(3):613–622. [PubMed: 21191404]
7. Skobowiat C, Dowdy JC, Sayre RM, Tuckey RC, Slominski A. Cutaneous hypothalamic-pituitary-adrenal axis homolog: regulation by ultraviolet radiation. Am J Physiol Endocrinol Metab. 2011; 301(3):E484–493. [PubMed: 21673307]
8. Blázquez C, Carracedo A, Barrado L, et al. Cannabinoid receptors as novel targets for the treatment of melanoma. FASEB J. 2006; 20(14):2633–2635. [PubMed: 17065222]

9. Grando SA, Pittelkow MR, Schallreuter KU. Adrenergic and cholinergic control in the biology of epidermis: physiological and clinical significance. J Invest Dermatol. 2006; 126(9):1948–1965. [PubMed: 16912692]
10. Slominski A, Tobin DJ, Zmijewski MA, Wortsman J, Paus R. Melatonin in the skin: synthesis, metabolism and functions. Trends Endocrinol Metab. 2008; 19(1):17–24. [PubMed: 18155917]
11. Bodo E, Kany B, Gáspár E, et al. Thyroid-stimulating hormone, a novel, locally produced modulator of human epidermal functions, is regulated by thyrotropin-releasing hormone and thyroid hormones. Endocrinology. 2010; 151(4):1633–1642. [PubMed: 20176727]
12. Cianfarani F, Baldini E, Cavalli A, et al. TSH receptor and thyroid-specific gene expression in human skin. J Invest Dermatol. 2010; 130(1):93–101. [PubMed: 19641516]
13. Slominski A, Wortsman J, Kohn L, et al. Expression of hypothalamic-pituitary-thyroid axis related genes in the human skin. J Invest Dermatol. 2002; 119(6):1449–1455. [PubMed: 12485453]
14. van Beek N, Bodó E, Kromminga A, et al. Thyroid hormones directly alter human hair follicle functions: anagen prolongation and stimulation of both hair matrix keratinocyte proliferation and hair pigmentation. J Clin Endocrinol Metab. 2008; 93(11):4381–4388. [PubMed: 18728176]
15. Slominski AT, Kim T-K, Chen JJ, et al. Cytochrome P450scc-dependent metabolism of 7-dehydrocholesterol in placenta and epidermal keratinocytes. Int J Biochem Cell Biol. 2012; 44:2003–2018. [PubMed: 22877869]
16. Slominski AT, Kim TK, Shehabi HZ, et al. In vivo evidence for a novel pathway of vitamin D(3) metabolism initiated by P450scc and modified by CYP27B1. FASEB J. 2012; 26(9):3901–3915. [PubMed: 22683847]
17. Bikle DD. Vitamin D metabolism and function in the skin. Mol Cell Endocrinol. 2011; 347(1–2): 80–89. [PubMed: 21664236]
18. Slominski AT, Zmijewski MA, Semak I, et al. Cytochromes P450 and Skin Cancer: Role of Local Endocrine Pathways. Anticancer Agents Med Chem. 2013 (Epub ahead of print). 10.2174/18715206113139990308
19. Slominski A, Zbytek B, Nikolakis G, et al. Steroidogenesis in the skin: Implications for local immune functions. J Steroid Biochem Mol Biol. 2013 (Epub ahead of print). 10.1016/j.jsbmb.2013.02.006
20. Skobowiat C, Nejati R, Lu L, Williams RW, Slominski AT. Genetic variation of the cutaneous HPA axis: an analysis of UVB-induced differential responses. Gene. 2013; 530(1):1–7. [PubMed: 23962689]