Neuroendocrinology of the skin
An overview and selective analysis

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Abbreviations: POMC, proopiomelanocortin; ACTH, adrenocorticotropic; α-MSH, α-melanocyte stimulating hormone; MC1R, melanocortin 1 receptor; UV, ultraviolet; VDR, vitamin D receptor; AC, adenylyl cyclase; ACTH, adrenocorticotropic hormone; AP-1, activator protein 1; CARE, Ca²⁺ response element; CRE, cAMP response element; CREB, cAMP response element binding protein; CRF (CRH), corticotropin-releasing factor (hormone); CRF1 (CRH-R1, CRHR1, CRFR1), corticotropin-releasing factor receptor type 1; GPCR, G-protein coupled receptor; HPA, hypothalamic-pituitary-adrenal axis; HPT, hypothalamic-pituitary-thyroid axis; IP3, inositol trisphosphate; MSH, melanocyte stimulating hormone; NFκB, nuclear factor κ-light-chain-enhancer of activated B cells; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; POMC, pro-opiomelanocortin; SNP, single nucleotide polymorphism; UCN-I, II, III, urocortins I, II and III

The concept on the skin neuro-endocrine has been formulated ten years ago, and recent advances in the field further strengthened this role. Thus, skin forms a bidirectional platform for a signal exchange with other peripheral organs, endocrine and immune systems or brain to enable rapid and selective responses to the environment in order to maintain local and systemic homeostasis. In this context, it is not surprising that the function of the skin is tightly regulated by systemic neuro-endocrine system. Skin cells and skin appendages not only respond to neuropeptides, steroids and other regulatory signals, but also actively synthesis variety of hormones. The stress responses within the skin are tightly regulated by locally synthesized factors and their receptor expression. There is growing evidence for alternative splicing playing an important role in stress signaling. Deregulation of the skin neuro-endocrine signaling can lead or/and be a marker of variety of skin diseases. The major problem in this area relates to their detailed mechanisms of crosstalk between skin and brain and between the local and global endocrine as well as immune systems.

Skin as an Neuro-Endocrine Organ

More than ten years ago a comprehensive model of the skin acting as neuro-endocrine organ has been proposed.¹ Although the concept is still evolving,¹⁻³ 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 (Fig. 1).¹ The skin is not only a classical source of vitamin D³ but also a place of synthesis and metabolism of several neuropeptides including elements of hypothalamic-pituitary-adrenal (HPA),¹⁻³⁾ and hypothalamic-pituitary-thyroid (HPT)¹⁺14,16 axes. Skin cells also possess functional seroton- in- and melatoninergic systems¹⁷⁻²² and express steroidogenic activity.¹,¹² The presence of several neuropeptides and other biologically active compounds in the skin is due to both their local synthesis and active transport from blood or release form nerves endings or migrating immune cells.¹,¹²⁻²³ The newly synthesized neuropeptides and hormones have predominantly local activity in paracrine or autocrine fashion, but there is a growing evidence that those regulatory substances once produced by skin can diffuse to the blood or activate local nerve endings within the dermis thus they may influence central organs including brain.¹,³

HPA axis. HPA axis is one of the most prominent central systems of regulation of stress response in animals. Its activation triggers the cascade of production and secretion of neurotransmitters, regulatory peptides and steroid hormones.²⁴ The first step of signaling cascade is the synthesis of corticotropin-releasing factor (CRF, CRH) in the hypothalamus followed by activation of CRF receptor type 1 (CRF1) in the anterior pituitary; subsequent production of proopiomelanocortin (POMC) and its further proteolytic processing to adrenocorticotropic (ACTH), α-melanocyte-stimulating hormone (MSH), lipotropins (LPH) and β-endorphin.²⁵ ACTH through the activation of melanocortin receptor type 2, MC2R receptor, stimulates production and secretion of steroids in adrenal glands. On the other hand MSH activates melanin synthesis in melanocytes by the interaction

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The skin cells and its appendages are the targets for CRF and related urocortins (I, II and III) bioregulation. Interestingly human epidermis expresses preferentially CRF1, while in rodents CRF2 prevails, what suggests that the expression of CRF2 might be important for hair physiology. 

In contrast to human skin the expression of CRF gene in mice was below level of detectably, but CRF immunoreactivity was found in mice skin and its was postulated that it originated from nerves ending. As described above CRF stimulates two types of receptor (CRF1 and CRF2), and the stimulation of CRF1 results in proopiomelanocortin (POMC) synthesis and its subsequent production of key regulator of steroid synthesis—ACTH and of melanogenesis α-MSH.

The cutaneous transcription and translation of the POMC with subsequent processing to final peptides were for the first time reported in rodent skin and later in human skin cells and skin biopsies. The presence of POMC and POMC-derived peptides including multiple forms of ACTH, MSH and β-endorphins were confirmed by means of western blotting, reverse phase HPLC and mass spectroscopy in multiple skin cells including: melanocytes, keratinocytes, immune cells infiltrating, hair follicle, sweat glands, melanocytic nevi and walls of blood vessels. In an addition production of CRF and POMC was also shown in UVB irradiated human melanocytes. In summary, the skin produced all crucial peptides of HPA axis.

The synthesis POMC and secretion of ACTH within the skin is the major stimulant of steroidogenesis. Skin indeed possesses fully functional enzymatic machinery for cutenous production of corticosterone and cortisol which includes adrenodoxin, adrenodoxin reductase, P450scc, P450c17 and P450c21. The production of corticosterone and cortisol was shown in dermal fibroblasts and normal and malignant epidermal melanocytes, but not in epidermal keratinocytes, what suggested cell type specific metabolic pathways corresponding to different structural compartments of the skin. The other products of corticosteroidogenesis in the skin are deoxycorticosterone (DOC), 18-hydroxy-DOC and others with the exception of aldosterone.

Human melanocytes and fibroblasts respond to CRF, ACTH and factors raising intracellular cAMP with an increased production of cortisol and/or corticosterone. This production was dependent on functional CRF1 and on POMC expression. The corticosterone and cortisol production in fibroblasts and melanocytes was stimulated by ACTH. Similar results on CRF and ACTH stimulate cortisol production was also described in the histocultured hair follicles. This suggests that in epidermal melanocytes and dermal fibroblasts HPA organization is conserved, while diverging in its distal step, where CRH and ACTH stimulate production of corticosterone, in addition to cortisol. It was also suggested that the HPA organization developed first in the integument and then was adopted by the central nervous and endocrine system during evolution of stress response system.

Skin equivalent of the HPA axis. The concept that skin expresses an equivalent of the HPA axis was presented for the first time almost 14 years ago. In fact, all skin cell lines (melanocytes, keratinocytes, fibroblasts, sebocytes and mast cells) do express CRF, related urocortins and the corresponding receptors of MC1R receptor. β-endorphin strongly binds to μ-opioid receptor and similarly to other opioids has analgesic and relaxing properties. Rising level of steroids in circulation attenuates inflammation and forms a back loop by inhibition of synthesis of CRF and POMC.

Figure 1. Skin neuroendocrine system regulates global (A and B) and local (B) homeostasis. In response to noxious stimuli, the skin mounts progressive, intensity-dependent, highly coordinated responses. The generated signals travel through humoral or neural pathways to reach the central nervous system, immune system, and other organs. Reproduced with permission Copyright 2000, The Endocrine Society.
Most recently we have discovered a new metabolic pathway initiated by CYP11A1 (a crucial enzyme of steroidogenesis), which by acting on 7-dehydrocholesterol \(^{47,55}\) or vitamins D \(^{56-59}\) and ergosterol, \(^{60}\) generate 5,7-dienals and hydroxyderivatives of vitamin D and ergosterol that are biologically active. \(^{55,61-64}\) The 5,7-dienals are transformed by UVB to the corresponding vitamin D compounds with short side chain. \(^{47,64,65}\)

**CRF as a regulator of skin functions.** The effects of CRF and related uroctins (I, II and III) on the skin cells and its appendages include: modulation of growth, immune function or synthesis of biologically active molecules. \(^{1,4,11,23,34-38,45,48,49,52,64,66-74}\)

Detailed studies performed on isolated skin cell lines revealed pleiotropic effects of CRF and related peptides (Fig. 2). In human epidermal melanocytes, for instance, CRF stimulates cell proliferation in serum supplemented cultures, but inhibitory effect was observed under serum deprived conditions. \(^{35}\) The effects of CRF are also cell type dependent, because proliferation of human dermal fibroblasts was stimulated, while the adverse effect was observed in human normal keratinocytes. \(^{35}\) Moreover in human epidermal keratinocytes and immortalized HaCaT keratinocytes, CRF stimulates cytokeratin 1 and involucrin synthesis, but inhibits cytokeratin 14 expression. This observation strongly suggests induction of differentiation pathway in those cells. \(^{64,69}\) CRF also exerts predominantly a proinflammatory effect by stimulation of secretion of interleukin 6 and 11 in human immortalized keratinocytes (HaCaT), \(^{72}\) which is in the agreement with the current model. The possible mechanism of induction of immune response is provided by observation that CRF stimulates translocation, inhibits degradation and induces transcriptional activity of master regulator of immune response—nuclear factor kappa B (NFkB) in human keratinocytes. \(^{70}\) On the other hand, CRF inhibits expression of adhesion molecule 1 (ICAM-1), human leukocytes antigen (HLA-DR) in normal skin keratinocytes. \(^{73}\) Moreover decreased level of IL-1β and interleukin 18 in immortalized HaCaT keratinocytes was observed after stimulation with CRF. \(^{36,72,73}\) In an addition CRF inhibits NFkB activity in human melanocytes \(^{66}\) and immortalized human keratinocytes (HaCaT). \(^{71}\)

It is clear that CRF and related peptides have significant impact on skin function but the results of stimulation are cell type, localization and condition dependent. The potential explanation of this phenomenon might deferential coupling to the signal transduction pathway in selected skin-derived cells or adnexal structures. It is well established that stimulation of CRH receptors results in activation of three main secondary messengers: cyclic AMP (cAMP), inositol-3-phosphate (IP3) and calcium (Fig. 2). Elevated level of secondary messengers (cAMP, IP3 and/or Ca\(^{2+}\)) in cells, results in activation of multiple transcriptional factors including cAMP response element (CREB), activator protein 1 (AP-1, induced by IP3), NFkB and the calcium response element (CARE) (reviewed in ref. 75). It was shown that expression of POMC and subsequent production of corticosterone in human dermal fibroblast is mediated by cAMP signaling. \(^{69}\) On the other hand CRF stimulation of activator protein-1 DNA-binding activity is a key factor required for inhibition of growth and stimulation of differentiation through G1 arrest in human epidermal keratinocytes. \(^{69}\) The effect of CRF on NFkB signaling pathway is mediated by POMC in human epidermal melanocytes where inhibition of NFkB was observed. \(^{66}\) The adverse (stimulatory) effect on NFkB was observed in human epidermal keratinocytes. \(^{70}\) Lastly, CRF and related peptides modulates hair pigmentation, but due to the presence of subpopulation of hair follicular melanocytes with different expression of CRF1 and CRF2 receptor results varies. \(^{57}\)

**Alternative splicing of the genes coding CRF receptors.** Despite of the significant progress in understanding of molecular mechanisms of CRF activity in skin the quest for potential factors responsible for its cell specific action is still on. Recently we postulated that such a variety of phenotypic effects of CRF may be explained by cell type dependent expression of multiple isoforms of the CRF receptors type 1 and 2. \(^{35,36,75-81}\) At least

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**Figure 2.** CRF1 receptor as the regulator of skin cells functions. Ligand binding to CRF1 receptor activates at least three Gα subunits (αq, αi and αs) of G-protein resulting in stimulation cAMP production by adenylate cyclase (AC) with subsequent cAMP-induced phosphorylation of CREB and activation of cAMP-responsive element (CRE). Mobilization of calcium (Ca\(^{2+}\)) results in activation of calcium-responsive element (CRE). Activation of AP can also trigger mitogen-activated protein kinases (MAPK) pathway through protein kinase A (PKA). In addition, αq-mediated stimulation of phospholipase C results in IP3-driven activation of Activator Protein 1 (AP-1) dependent promoters. Downstream signaling from CRF1 receptor regulates expression of several genes including POMC, several interleukins, involucrin and cytoketerin 14. The phenotypic effects of stimulation include: stimulation of differentiation, steroidogenesis, melanogenesis and release of arachidonic acid. CRF inhibits cell division and regulates immune response. See text and citations within for details in Zmijewski et al. \(^{75}\) Reproduced with permission from Acta Biochim Pol.
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The skin is a rich source of melatoninergic system. Melatonin is a major pineal hormone with activity of a neurotransmitter, cytokine, antioxidant and global regulator of circadian clock. It synthesis is not restricted to pineal gland, but was detected in several organs including skin. The skin possesses fully functional biochemical machinery for melatonin synthesis. The skin cells not only possess two key enzymes taking part in hydroxylation of L-tryptophan to 5-hydroxytryptophan, but also have a sufficient capacity for synthesis and regeneration of 6-tetrahydrobiopterin (6BH4) an essential cofactor for regeneration of TPH. Melatonin undergoes decarboxylation by aromatic L-amino acid decarboxylase (AAD) what leads to serotonin synthesis. Serotonin is then acetylated by arylalkylamine N-acetyltransferase (AANAT) and/or arylamine N-acetyltransferase (NAT). The AANAT is wildly expressed epidermis and adnexal structures and NAT presence was detected in rodent and human skin by combination of identify by high-performance liquid chromatography HPLC and mass spectrometry (MS). It seems that both extrapineal AANAT and NAT at least in part participate in synthesis of NAS in skin of mouse model of AANAT deficiency. The last step of synthesis of melatonin is catalyzed by hydroxyindol methyltransferese (HIOMT) and the expression of HIOMT and its enzymatic activity was detected in epidermal and dermal cells of human and rodent origin.

In summary, epidermal and dermal cells as well as skin appendages are capable for synthesis of two major regulator melatonin and serotonin. Moreover human skin is also a place of metabolism of melatonin with creation of the series of derivatives of potential physiological significance.

eight CRF1 isoforms, namely α, β, c, d, e, f, g, h was detected in human skin and a few additional in rodents. Current model, presented on Figure 3, suggests the central role of CRF1α and the other CRF1 isoforms modulate signaling and/or localization of receptor by dimer formation, different substrate affinity (Fig. 3). The soluble isoform h, being secreted from cells might represent so called decoy receptor, which can lower the concentration of free CRF available for membrane-bound receptors. The co-expression of CRF1 isoforms can result both in attenuation of CRF signals or their modulation as proposed in reference 75, 78–80 (Fig. 3). In SKMEL-188 melanoma cells express exclusively the CRF1d isoform, coupling to cAMP was impaired, but CRF strongly stimulated Ca2+ flux suggesting activation voltage-activated Ca2+ ion channels or PLC.

Melatonieric system in the skin. Melatonin is a major pineal hormone with activity of a neurotransmitter, cytokine, antioxidant and global regulator of circadian clock. It synthesis is not restricted to pineal gland, but was detected in several organs including skin.

Figure 3. Putative mechanism regulating expression of different isoforms of CRF1 in skin cells. CRF1 gene contains 14 exons and only one isoform of receptor-CRF1β (also called pro-CRF1) is coded by all exons. CRF1 transcript is also subjected to alternative splicing resulting in at least 8 isoforms. Recent studies showed that expression and/or co-expression of CRF1 isoforms is responsible for modulation of CRF1 signaling. Plus indicates stimulation of downstream signaling by the classic pathway (CRF1α) or alternative pathway (CRF1β). Soluble isoforms (CRF1e and h) were also found to stimulate CRF signaling when co-expressed with CRF1α. Minus indicates inhibition of CRF signaling on different levels including: fast mRNA decay (CRF1e), dimerization and subsequent intercellular retention resulting in most probable premature receptor degrada-
tion (CRF1e with CRF1d, CRF1f or CRF1g), decoy receptor mechanism (CRF1h and e when secreted), agonist binding impairment (CRF1c) or G-protein binding inhibition (CRF1d). Reproduced with permission.
Figure 4. Synthesis of melatonin in the skin. Biochemical pathway of melatonin synthesis in the skin. The cutaneous melatonin biosynthetic pathway starts with hydroxylation of tryptophan (I) by tryptophan-5-hydroxylase (TPH). In skin cells, the reaction is catalyzed predominantly by TPH1, shown in the western blot insert (A), which is an enzyme of approximately 50 kD (arrowhead in insert) that is processed and/or degraded to lower molecular weight species (asterisk in insert). TPH is immunolocalized in the epidermis (E), hair follicle (ORS) and eccrine glands (EG), showing the highest expression in melanocytes (arrows) (A and B). 5-hydroxytryptophan (II) is further decarboxylated by aromatic amino acid decarboxylase (AAD). The product, serotonin (III), is acetylated by serotonin-N-acetyltransferase(s) (AANAAT, NAT), which is expressed in cells of epidermal, dermal and adnexal compartments (E, blood vessel (BV), EG and hair follicle structures (C)). The final synthesis step is carried out by 4-hydroxyindole-O-methyl transferase (HIOMT), which converts N-acetylserotonin (IV) into melatonin (V), although this conversion can be reversed by CYP450 (CYP2C19). Immunocytochemical localization of melatoninlike immunoreactivity is shown (D) [upper E, BV and mast cells (MCs)]. Immunocytochemistry was performed on human-skin biopsies and primary-antibody staining was visualized with aminoethylcarbazole (AEC). For technical details see reference 18. D, dermis; FP: hair follicle papilla; HF ORS: hair follicle outer-root sheath; MX: hair follicle matrix. Reprinted from Slominski et al.17 with permission from Elsevier.
to classic enzymatic pathway leading to formation of 6-hydroxy melatonin and subsequent synthesis of 5-methoxyindole acetate or 5-methoxytryptophol, the skin cell products N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) (reviewed in ref. 17, 18 and 22). This highly active melatonin derivative is produced as a non-enzymatic reaction driven by reactive oxidative species (ROS). This reaction is of special interest because skin is constantly subjected to ROS generated during exposure to UV irradiation and/or as a side effect of melanogenesis. Both melatonin and AFMK seems to possess direct (receptor independent) protective effect against oxidative damage in human skin which might be used in both protection and therapy.\textsuperscript{17,22}

Receptor and non-receptor mediated activity of melatonin in the skin. The expression of the membrane-bound melatonin receptors MT1 and MT2 in the skin is cell type or compartment specific.\textsuperscript{18,20,22,93} In human skin both receptors are expressed but MT1 seems to be predominant receptor found in both whole skin samples and cultured cells.\textsuperscript{17,18,22} Expression of MT2 receptor is strongly correlated with hair follicles (as studied on C57BL/6 mouse model) and its expression is regulated by hair-cycle phase with maximum expression in catagen.\textsuperscript{17,93,94}

The expression of melatonin membrane receptors is regulated also by environmental factors (UVB), underlying pathology (skin cancer) and genetic background including alternative splicing of receptors.\textsuperscript{18} The ROR\textsubscript{a} is member of orphan nuclear receptor which can bind melatonin and its expression was shown in several skin cell lines including melanoma cells.\textsuperscript{18,95} The transcript for ROR\textsubscript{a} undergoes posttranscriptional modifications with at least 4 alternative splicing variants of mRNA. The ROR\textsubscript{a} is widely expressed in human and rodents skin but the expression and alternative splicing is cell-type dependent and could be modulated by physiological (exposure to UVB) or pathological (malignant melanoma progression) factors.\textsuperscript{17,18,22} Additionally, the ROR\textsubscript{a} transcription pattern correlates significantly with hair growth-cycle phase as studied in mouse skin.\textsuperscript{24}

Melatonin expresses pluripotent activity in the skin including modulation of melanogenesis, modulation of proliferation and general protection.\textsuperscript{17,18,22,28,94,96,97} The effect of melatonin on fur pigmentation is especially pronounced in mammals subjected to a seasonal color changes.\textsuperscript{28,97} It was shown to inhibit melanoma growth\textsuperscript{95,98} but also melatonin showed protective effects on human keratinocytes subjected to UV irradiation.\textsuperscript{17,22,29,100} This duality might be explained by the variety of possible intracellular pathway triggered by melatonin including 2 membrane bound receptors (MT1 and MT2), nuclear receptors (ROR\textsubscript{x} isoforms) and its direct antioxidative effects. Moreover, recently additional melatonin binding protein (former MT3 receptor) was identified as quinone reductase type II what broaden the spectrum of melatonin targets within the skin where NQO2 is wildly expressed.\textsuperscript{18,95}

Perspectives

In this overview we have summarized only two major aspect of neuroendocrine regulation in the skin, namely analogue of HPA axis and melatooninergic system in the skin. Last ten years generated major advances in understanding of molecular background of the hormonal regulation in the skin and its importance in normal physiology and pathology.\textsuperscript{2,6,4,101} Recent studies showed importance and molecular mechanism of activity of other hormones and in regulation of skin physiology including novel vitamin D derivatives and steroids with unsaturated B ring,\textsuperscript{55,63,64} hypothalamus-pituitary-thyroid axis elements\textsuperscript{3,16} and enkephalin.\textsuperscript{102} The expression and production of neuropeptides, growth factors, cytokines, steroids, other regulatory molecules and their receptors gives the skin independence and allows the local response to the environmental stimuli. The independence does not essentially exclude the crosstalk between the skin and central nervous, immune systems and other endocrine organs.

The exploration of the interaction between skin cells and other organ is the major future challenge. We have proposed more than 16 years ago that melanocytes govern endocrine activity of epidermis.\textsuperscript{103-106} Melanocytes are in constant and direct connection with skin keratinocytes through its processes and secretion of regulatory molecules.\textsuperscript{6} There is also a signal exchange between epidermis and dermis. The resident immune cells in dermis (mast cells) are perfect candidates for signal amplifiers.\textsuperscript{107,108} Mast cells respond to hormonal stimulation and react by degranulation releasing not only histamine and tryptase but also several neuropeptides including CRF. Due to their location in close proximity to the nerve ending and blood vessels the signaling from and to the skin might be simple passed or modulated and multiplied. Such as communication, once studied in detail will have a direct used in diagnostic and treatment of several immune, neuroimmune and autoimmune diseases and pathological conditions of skin including, acne, psoriasis, alopecia or vitiligo.

As exemplified here by CRF1 isoforms, an alternative splicing of receptor coding genes is becoming an important player in the local regulation of physiological activity and stress response in the skin, but the detail molecular mechanism and splicing factors involved remains largely unknown.

In summary, skin is our largest organs, separating internal milieu from environmental insults, thus even local expression and production of neuropeptides or hormones may have a significant impact on global homoeostasis. Thus the crosstalk between epidermis, dermis and internal organs as well as brain and endocrine organs should be of special interest.

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free radical scavenging to DNA damage repair. Exp Fischer

Nor Physiol 2003; 196:144-53.

S, Wortsman J. Functional activity of serotoninergic

melatoninergic systems are fully expressed in human


Smith AI, Funder JW. Proopiomelanocortin processing in the pituitary, central nervous system and peripheral tissues. Endocrin Rev 1988; 9:159-79.


Slominski A, Baker J, Ermak G, Chakraborty A, Pawelej K. Ultraviolet B stimulates production of corti-


Slominski A, Mazurkiewicz JE, Wortsman J. Liquid chromatography-mass spectrometry detection of corti-

Slominski A, Szeiczewski A, Wortsman J. Liquid chromatography-mass spectrometry detection of corti-


References


4. Slominski A, Wortsman J, Linton E, Piarschik A, Zbytek B. The skin as a model for the immuno-


Regulation of Peripheral Inflammation by the CNS. Basel, Bosten, Birkhaeuser Verlag 2003; 149-76.

5. Slominski A, Wortsman J. Self-regulated endocrine sys-


6. Slominski A. Neuroendocrine activity of the melano-


mal functions, is regulated by thyrotropin-releasing hormone and thyroid hormones. Endocrinology 2010; 151:1633-42.


17. Slominski A, Tobin DJ, Zmijewski MA, Wortsman J, Pau R. Melatonin in the skin: synthesis, metabo-


