REPORT

Dermato-Endocrinology 3:1, 3-10; January/February/March 2011; © 2011 Landes Bioscience

Neuroendocrinology of the skin
An overview and selective analysis

Michal A. Zmijewski[1] and Andrzej T. Slominski[2,*]

[1]Department of Histology; Medical University of Gdańsk; Gdańsk, Poland; [2]Department of Pathology and Laboratory Medicine; Center for Cancer Research; University of Tennessee Health Science Center; Memphis, TN USA

Key words: skin, stress, homeostasis, hormones, neurotransmitters, regulatory network, corticotropin releasing factor (CRF), melatonin, POMC

Abbreviations: POMC, proopiomelanocortin; ACTH, adenocorticotropin; α-MSH, α-melanocyte stimulating hormone; MC1R, melanocortin 1 receptor; UV, ultraviolet; VDR, vitamin D receptor; AC, adenylate cyclase; ACTH, adrenocorticotropic hormone; AP-1, activator protein 1; CARE, Ca^{2+} 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 homone; 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,[1-7] 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 D[8] but also a place of synthesis and metabolism of several neuropeptides including elements of hypothalamic-pituitary-adrenal (HPA),[1,9-12] and hypothalamic-pituitary-thyroid (HPT),[13-16] axes. Skin cells also possess fully functional serotonin- and melatoninergic systems[17-22] 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.[1-3,23] 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[25,26] followed by activation of CRF receptor type 1 (CRF1) in the anterior pituitary; subsequent production of proopiomelanocortin (POMC) and its further proteolytic processing to adrenocorticotropin (ACTH), α-melanocyte-stimulating hormone (MSH), lipotropins (LPH) and β-endorphin.[27] 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

*Correspondence to: Andrzej Slominski; Email: aslominski@uthsc.edu
Submitted: 11/12/10; Accepted: 12/21/10
DOI: 10.4161/derm.3.1.14617

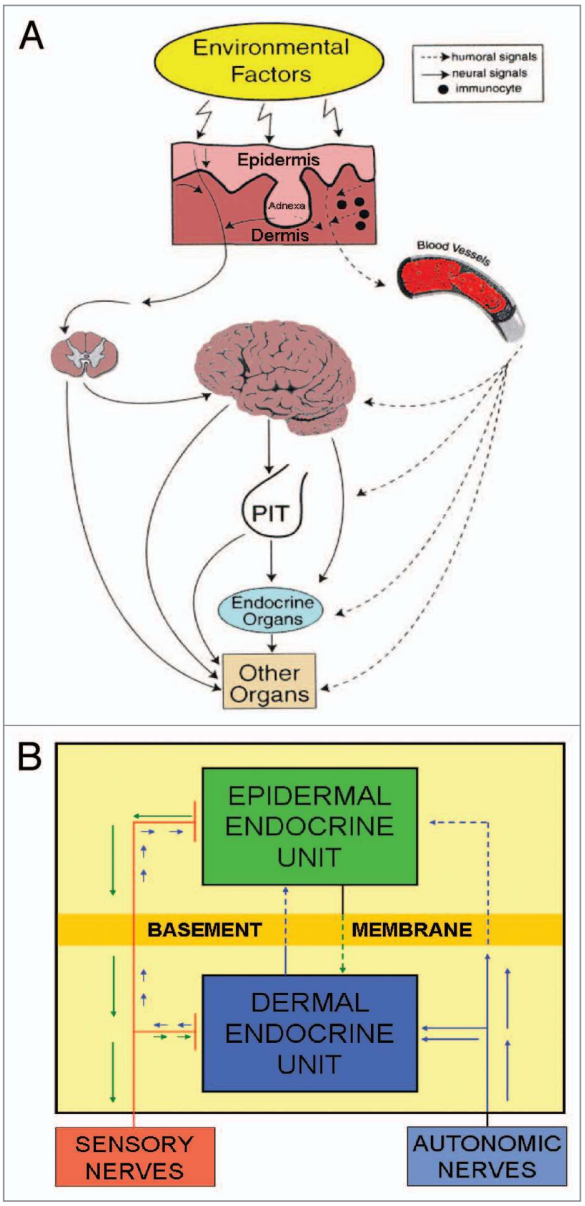

Figure 1. Skin neuroendocrine system regulates global (A and B) and local (B) homeostasis. In response to noxious stimuli, the skin mounts progressive, intensity-dependent, highly coordinated responses. The generated signals travel through humoral or neural pathways to reach the central nervous system, immune system, and other organs. Reproduced with permission[1] Copyright 2000, The Endocrine Society.

of MC1R receptor.[18,28] 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.[24]

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.[10,29] In fact, all skin cell lines (melanocytes, keratinocytes, fibroblasts, sebocytes and mast cells) do express CRF, related urocortins and the corresponding receptors for corticotropin-releasing factor (CRF1-CRH-R1 or CRF2-CRH-R2).[1,11,23,30-38] Thus, 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.[12,32]

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.[11,23] On the other hand mouse skin efficiently expresses urocortin.[33] 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.[12]

The cutaneous transcription and translation of the POMC with subsequent processing to final peptides were for the first time reported in rodent skin[39,40] and later in human skin cells[41] and skin biopsies.[9,42] 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.[1,34,43,44] In an addition production of CRF and POMC was also shown in UVB irradiated human melanocytes.[30,45,46] 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.[12,24] Skin indeed possesses fully functional enzymatic machinery for cutenous production of corticosterone and cortisol which includes including adrenodoxin, adrenodoxin reductase, P450scc, P450c17 and P450c21.[29,47] The production of corticosterone and cortisol was shown in dermal fibroblasts and normal and malignant epidermal melanocytes,[48-51] as well as in hair follicle including follicular keratinocytes,[52] 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.[51,53,54]

Human melanocytes and fibroblasts respond to CRF, ACTH and factors raising intracellular cAMP with an increased production of cortisol and/or corticosterone.[48,49] This production was dependent on functional CRF1 and on POMC expression. The corticosterone and cortisol production in fibroblasts and melanocytes was stimulated by ACTH.[48,49] Similar results on CRF and ACTH stimulate cortisol production was also described in the histocultured hair follicles.[52] 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.[2,12] 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.[7]

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-dienal steroids and hydroxyderivatives of vitamin D and ergosterol that are biologically active.[55,61-64] The 5,7-dienal steroids 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 urocortins (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.[68,69] 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 (NFκB) 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 NFκB 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 (IP_3) and calcium (**Fig. 2**). Elevated level of secondary messengers (cAMP, IP_3 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 IP_3), NFκB and the calcium response element (CARE) (reviewed in ref. 75). It was shown that expression of POMC and subsequent production of cortiosterone in human dermal fibroblast is mediated by cAMP signaling.[49] 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 G_0/1 arrest in human epidermal keratinocytes.[69] The effect of CRF on NFκB signaling pathway is mediated by POMC in human epidermal melanocytes where inhibition of NFκB was observed.[66] The adverse (stimulatory) effect on NFκB 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.[67]

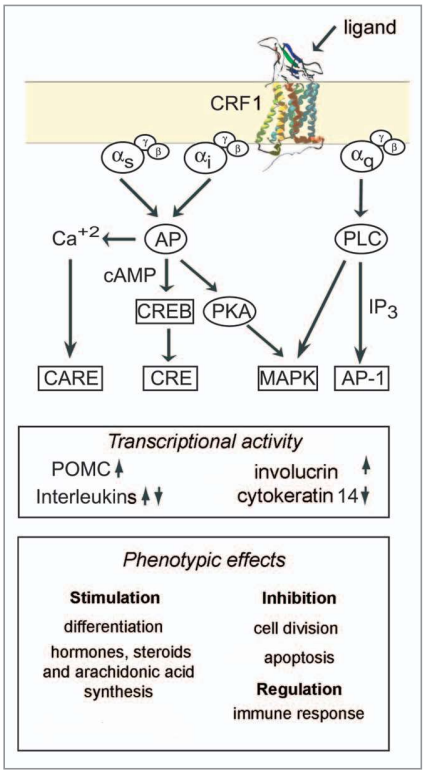

Figure 2. CRF1 receptor as the regulator of skin cells functions. Ligand binding to CRF1 receptor activates at least three Gα subunits (α_s, α_i and α_q) of G-protein resulting in stimulation cAMP production by adenylate cyclase (AC) with subsequent cAMP-induced phosphorylation of CREB and activation of cAMP-responsive element (CRE). Mobilization of calcium (Ca^{+2}) results in activation of calcium-responsive element (CARE). Activation of AP can also trigger mitogen-activated protein kinases (MAPK) pathway through protein kinase A (PKA). In addition, α_q-mediated stimulation of phospholipase C results in IP_3-driven activation of Activator Protein 1 (AP-1) dependent promoters. Downstream signaling from CRF1 receptor regulates expression of several genes including POMC, several interleukins, involucrine and cytokeratin 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.

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.[32,36,75-81] At least

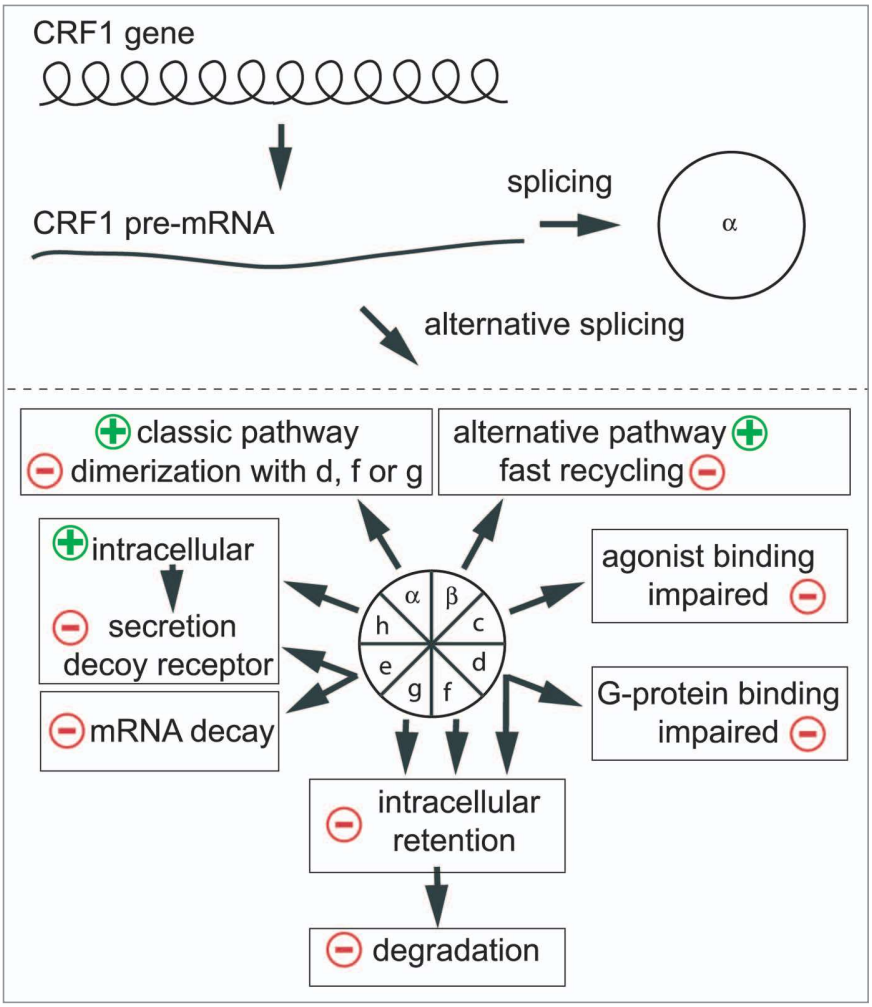

Figure 3. Putative mechanism regulating expression of different isforms of CRF1 in skin cells. CRF1 gene contains 14 exons and only one isoform of receptor-CRF1β (also called pro-CRF1) is coded by all exons. CRF1 transcript is also subjected to alternative splicing resulting in at least 8 isoforms. Recent 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 degradation (CRF1α with CRF1d, CRFf or CRFg), decoy receptor mechanism (CRF1h and e when secreted), agonist binding impairment (CRF1c) or G-protein binding inhibition (CRF1d). Reproduced with permission.[75]

eight CRF1 isoforms, namely α, β, c, d, e, f, g, h was detected in human skin[76] and a few additional in rodents.[76,77] 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[36,78,79,80] (**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. [36,78,79] 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 Ca^{2+} flux suggesting activation voltage-activated Ca^{2+} ion channels or PLC.[35,36,80]

Melatoninergic system in the skin. Melatonin is a major pineal hormone with activity of a neurotransmitter, cytokine, antioxidant and global regulator of circadian clock.[17,20] It synthesis is not restricted to pineal gland, but was detected in several organs including skin, retinal pigment epithelial cells, brain, Harderian gland, ciliary body, lens, retina, airway epithelium, bone marrow, thymus, immune cells, gonads, placenta, gastro-intestinal tract and skin.[17,18,82-84] The skin possesses fully functional biochemical machinery for melatonin synthesis (**Fig. 4**). The multistep reaction follows the classical metabolic pathway and starts with hydroxylation of L-tryptophan by tryptophan hydroxylase 1 (TPH1).[18-20,85] Interestingly, recently described TPH2 preferentially expressed in the brain,[86] was also detected in normal melanocytes and melanomas (Zmijewski MA and Slominski A, unpublished). 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 ($6BH_4$)—an essential cofactor for regeneration of TPH.[87] 5-hydroxytryptophan undergoes decarboxylation by aromatic L-amino acid decarboxylase (AAD) what leads to serotonin synthesis.[17] Serotonin is then acetylated by arylalkylamine N-acetyltransferase (AANAT) and/or arylamine N-acetyltransferase (NAT).[17-20,22,84,88,89] The AANAT is wildly expressed epidermis and adnexal structures (**Fig. 4**) 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.[11,20,90] The last step of synthesis of melatonin is catalyzed by hydroxyindol metyltransferese (HIOMT) and the expression of HIOMT and its enzymatic activity was detected in epidermal and dermal cells of human and rodent origin.[18-20]

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.[84,91,92] In the addition

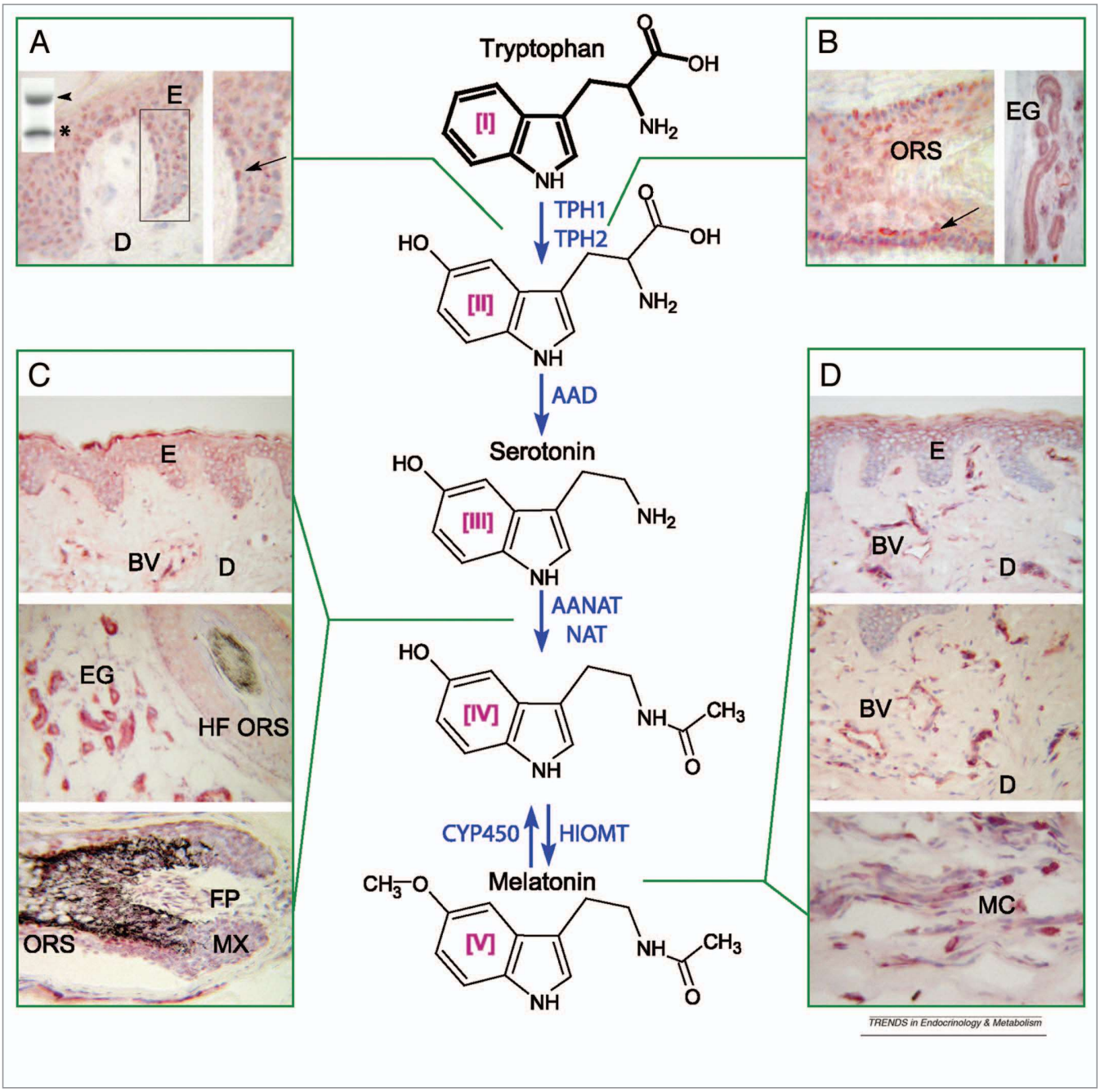

Figure 4. Synthesis of melatonin in the skin. Biochemical pathway of melatonin synthesis in the skin. The cutaneous melatonin biosynthetic pathway starts with hydroxylation of tryptophan (I) by tryptophan-5-hydroxylase (TPH). In skin cells, the reaction is catalyzed predominantly by TPH1, shown in the 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) (AANAT, 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.[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.[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.[17,18,20] 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.[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.[18] The RORa is member of orphan nuclear receptor which can bind melatonin and its expression was shown in several skin cell lines including melanoma cells.[18,95] The transcript for ROR1a undergoes posttranscriptional modifications with at least 4 alternative splicing variants of mRNA. The ROR1a 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.[17,18,22] Additionally, the RORa transcription pattern correlates significantly with hair growth-cycle phase as studied in mouse skin.[94]

Melatonin expresses pluripotent activity in the skin including modulation of melanogenesis, modulation of proliferation and general protection.[17,18,22,28,94,96,97] The effect of melatonin on fur pigmentation is especially pronounced in mammalians subjected to a seasonal color changes.[28,97] It was shown to inhibit melanoma growth[95,98] but also melatonin showed protective effects on human keratinocytes subjected to UV irradiation.[17,22,99,100] 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 (RORα 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.[18,95]

Perspectives

In this overview we have summarized only two major aspect of neuroendocine regulation in the skin, namely analogue of HPA axis and melatoninoergic 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.[2,6,64,101] 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,[55,63,64] hypothalamus-pituitary-thyroid axis elements[13-16] and enkefalin.[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.[103-106] Melanocytes are in constant and direct connection with skin keratinocytes through its processes and secretion of regulatory molecules.[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.[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.

Acknowledgements

The work was supported by National Science Foundation grant # IOS-0918934 (A.T.S.), National Institutes of Health grant # AR052190 (A.T.S.) and Polish Ministry of Science and Higher Education, project no. N405 623238 (M.A.Z.).

References

1. Slominski A, Wortsman J. Neuroendocrinology of the skin. Endocr Rev 2000; 21:457-87.
2. Slominski A, Wortsman J, Paus R, Elias PM, Tobin DJ, Feingold KR. Skin as an endocrine organ: implications for its function. Drug Discov Today Dis Mech 2008; 5:137-44.
3. Slominski A. Neuroendocrine system of the skin. Dermatology 2005; 211:199-208.
4. Slominski A, Wortsman J, Linton E, Pisarchik A, Zbytek B. The skin as a model for the immunomodulatory effects of corticotropin-releasing hormone. In: Schaefer M, Stein C, Ed. Mind over Matter—Regulation of Peripheral Inflammation by the CNS. Basel, Boston, Berlin: Birkhaeuser Verlag 2003; 149-76.
5. Slominski A, Wortsman J. Self-regulated endocrine systems in the skin. Minerva Endocrinol 2003; 28:135-43.
6. Slominski A. Neuroendocrine activity of the melanocyte. Exp Dermatol 2009; 18:760-3.
7. Slominski A. A nervous breakdown in the skin: stress and the epidermal barrier. J Clin Invest 2007; 117:3166-9.
8. Holick MF. Vitamin D: Evolutionary, Physiological and Health Perspectives. Curr Drug Targets.
9. Slominski A, Paus R, Wortsman J. On the potential role of proopiomelanocortin in skin physiology and pathology. Mol Cell Endocrinol 1993; 93:1-6.
10. Slominski A, Mihm MC. Potential mechanism of skin response to stress. Int J Dermatol 1996; 35:849-51.
11. Slominski AT, Botchkarev V, Choudhry M, Fazal N, Fechner K, Furkert J, et al. Cutaneous expression of CRH and CRH-R. Is there a "skin stress response system?" Ann NY Acad Sci 1999; 885:287-311.
12. Slominski A, Wortsman J, Tuckey RC, Paus R. Differential expression of HPA axis homolog in the skin. Mol Cell Endocrinol 2007; 265:143-9.
13. Slominski A, Wortsman J, Kohn L, Ain KB, Venkataraman GM, Pisarchik A, et al. Expression of hypothalamic-pituitary-thyroid axis related genes in the human skin. J Invest Dermatol 2002; 119:1449-55.
14. Bodo E, Kany B, Gaspar E, Knuver J, Kromminga A, Ramot Y, 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; 151:1633-42.
15. Cianfarani F, Baldini E, Cavalli A, Marchioni E, Lembo L, Teson M, et al. TSH receptor and thyroid-specific gene expression in human skin. J Invest Dermatol 2010; 130:93-101.
16. Gaspar E, Hardenbicker C, Bodo E, Wenzel B, Ramot Y, Funk W, et al. Thyrotropin releasing hormone (TRH): a new player in human hair-growth control. Faseb J 2010; 24:393-403.
17. Slominski A, Tobin DJ, Zmijewski MA, Wortsman J, Paus R. Melatonin in the skin: synthesis, metabolism and functions. Trends Endocrinol Metab 2008; 19:17-24.
18. Slominski A, Wortsman J, Tobin DJ. The cutaneous serotoninergic/melatoninergic system: securing a place under the sun. Faseb J 2005; 19:176-94.
19. Slominski A, Pisarchik A, Semak I, Sweatman T, Wortsman J, Szczesniewski A, et al. Serotoninergic and melatoninergic systems are fully expressed in human skin. Faseb J 2002; 16:896-8.
20. Slominski A, Pisarchik A, Zbytek B, Tobin DJ, Kauser S, Wortsman J. Functional activity of serotoninergic and melatoninergic systems expressed in the skin. J Cell Physiol 2003; 196:144-53.
21. Nordlind K, Azmitia EC, Slominski A. The skin as a mirror of the soul: exploring the possible roles of serotonin. Exp Dermatol 2008; 17:301-11.
22. Fischer TW, Slominski A, Zmijewski MA, Reiter RJ, Paus R. Melatonin as a major skin protectant: from free radical scavenging to DNA damage repair. Exp Dermatol 2008; 17:713-30.
23. Slominski A, Wortsman J, Pisarchik A, Zbytek B, Linton EA, Mazurkiewicz JE, et al. Cutaneous expression of corticotropin-releasing hormone (CRH), urocortin and CRH receptors. Faseb J 2001; 15:1678-93.
24. 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; 80:979-1020.
25. Vale W, Spiess J, Rivier C, Rivier J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 1981; 213:1394-7.
26. Chrousos GP. The Hypothalamic-Pituitary-Adrenal Axis and Immune-Mediated Inflammation. N Engl J Med 1995; 332:1351-63.
27. Smith AI, Funder JW. Proopiomelanocortin processing in the pituitary, central nervous system and peripheral tissues. Endocr Rev 1988; 9:159-79.
28. Slominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. Physiol Rev 2004; 84:1155-228.
29. Slominski A, Ermak G, Mihm M. ACTH receptor, CYP11A1, CYP17 and CYP21A2 genes are expressed in skin. J Clin Endocrinol Metab 1996; 81:2746-9.
30. Slominski A, Baker J, Ermak G, Chakraborty A, Pawelek J. Ultraviolet B stimulates production of corticotropin releasing factor (CRF) by human melanocytes. FEBS Lett 1996; 399:175-6.
31. Slominski A, Ermak G, Mazurkiewicz JE, Baker J, Wortsman J. Characterization of corticotropin-releasing hormone (CRH) in human skin. J Clin Endocrinol Metab 1998; 83:1020-4.
32. Slominski A, Pisarchik A, Tobin DJ, Mazurkiewicz JE, Wortsman J. Differential expression of a cutaneous corticotropin-releasing hormone system. Endocrinology 2004; 145:941-50.
33. Slominski A, Roloff B, Curry J, Dahiya M, Szczesniewski A, Wortsman J. The skin produces urocortin. J Clin Endocrinol Metab 2000; 85:815-23.
34. Slominski 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; 85:3582-8.
35. Slominski A, Zbytek B, Pisarchik A, Slominski RM, Zmijewski MA, Wortsman J. CRH functions as a growth factor/cytokine in the skin. J Cell Physiol 2006; 206:780-91.
36. Slominski A, Zbytek B, Zmijewski M, Slominski RM, Kauser S, Wortsman J, et al. Corticotropin releasing hormone and the skin. Front Biosci 2006; 11:2230-48.
37. Zouboulis CC, Seltmann H, Hiroi N, Chen W, Young M, Oeff M, et al. Corticotropin-releasing hormone: an autocrine hormone that promotes lipogenesis in human sebocytes. Proc Natl Acad Sci USA 2002; 99:7148-53.
38. Ito N, Ito T, Betterman A, Paus R. The human hair bulb is a source and target of CRH. J Invest Dermatol 2004; 122:235-7.
39. Slominski A, Paus R, Mazurkiewicz J. Proopiomelanocortin expression in the skin during induced hair growth in mice. Experientia 1992; 48:50-4.
40. Slominski A. POMC gene expression in hamster and mouse melanoma cells. FEBS Lett 1991; 291:165-8.
41. Schauer E, Trautinger F, Kock A, Schwarz A, Bhardwaj R, Simon M, et al. Proopiomelanocortin-derived peptides are synthesized and released by human keratinocytes. J Clin Invest 1994; 93:2258-62.
42. Slominski A, Ermak G, Hwang J, Chakraborty A, Mazurkiewicz JE, Mihm M. Proopiomelanocortin, corticotropin releasing hormone and corticotropin releasing hormone receptor genes are expressed in human skin. FEBS Lett 1995; 374:113-6.
43. Slominski A. Identification of beta-endorphin, alpha-MSH and ACTH peptides in cultured human melanocytes, melanoma and squamous cell carcinoma cells by RP-HPLC. Exp Dermatol 1998; 7:213-6.
44. Slominski A, Heasley D, Mazurkiewicz JE, Ermak G, Baker J, Carlson JA. Expression of proopiomelanocortin (POMC)-derived melanocyte-stimulating hormone (MSH) and adrenocorticotropic hormone (ACTH) peptides in skin of basal cell carcinoma patients. Hum Pathol 1999; 30:208-15.
45. Zbytek B, Wortsman J, Slominski A. Characterization of a ultraviolet B-induced corticotropin-releasing hormone-proopiomelanocortin system in human melanocytes. Mol Endocrinol 2006; 20:2539-47.
46. Chakraborty AK, Funasaka Y, Slominski A, Bolognia J, Sodi S, Ichihashi M, et al. UV light and MSH receptors. Ann NY Acad Sci 1999; 885:100-16.
47. Slominski A, Zjawiony J, Wortsman J, Semak I, Stewart J, Pisarchik A, et al. A novel pathway for sequential transformation of 7-dehydrocholesterol and expression of the P450scc system in mammalian skin. Eur J Biochem 2004; 271:4178-88.
48. Slominski A, Zbytek B, Szczesniewski A, Semak I, Kaminski J, Sweatman T, et al. CRH stimulation of corticosteroids production in melanocytes is mediated by ACTH. Am J Physiol Endocrinol Metab 2005; 288:701-6.
49. 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.
50. Slominski A, Zbytek B, Szczesniewski A, Wortsman J. Cultured human dermal fibroblasts do produce cortisol. J Invest Dermatol 2006; 126:1177-8.
51. Slominski A, Gomez-Sanchez CE, Foecking MF, Wortsman J. Metabolism of progesterone to DOC, corticosterone and 18OHDOC in cultured human melanoma cells. FEBS Lett 1999; 455:364-6.
52. Ito N, Ito T, Kromminga A, Bettermann A, Takigawa M, Kees F, et al. Human hair follicles display a functional equivalent of the hypothalamic-pituitary-adrenal axis and synthesize cortisol. Faseb J 2005; 19:1332-4.
53. Slominski A, Gomez-Sanchez CE, Foecking MF, Wortsman J. Active steroidogenesis in the normal rat skin. Biochim Biophys Acta 2000; 1474:1-4.
54. Slominski A, Wortsman J, Foecking MF, Shackleton C, Gomez-Sanchez C, Szczesniewski A. Gas chromatography/mass spectrometry characterization of corticosteroid metabolism in human immortalized keratinocytes. J Invest Dermatol 2002; 118:310-5.
55. Slominski AT, Zmijewski MA, Semak I, Sweatman T, Janjetovic Z, Li W, et al. Sequential metabolism of 7-dehydrocholesterol to steroidal 5,7-dienes in adrenal glands and its biological implication in the skin. PLoS One 2009; 4:4309.
56. Slominski A, Semak I, Zjawiony J, Wortsman J, Li W, Szczesniewski A, et al. The cytochrome P450scc system opens an alternate pathway of vitamin D3 metabolism. FEBS J 2005; 272:4080-90.
57. Tuckey RC, Li W, Zjawiony JK, Zmijewski MA, Nguyen MN, Sweatman T, et al. Pathways and products for the metabolism of vitamin D3 by cytochrome P450scc. FEBS J 2008; 275:2585-96.
58. Tuckey RC, Janjetovic Z, Li W, Nguyen MN, Zmijewski MA, Zjawiony JK, et al. Metabolism of 1alfa-hydroxyvitamin D3 by cytochrome P450scc to biologically active 1alfa,20-dihydroxyvitamin D3. J Steroid Biochem Molec Biol 2008; 112:213-9.
59. Slominski A, Semak I, Wortsman J, Zjawiony J, Li W, Zbytek B, et al. An alternative pathway of vitamin D2 metabolism. Cytochrome P450scc (CYP11A1)-mediated conversion to 20-hydroxyvitamin D2 and 17,20-dihydroxyvitamin D2. FEBS Journal 2006; 273:2891-901.
60. Slominski A, Semak I, Zjawiony J, Wortsman J, Gandy MN, Li J, et al. Enzymatic metabolism of ergosterol by cytochrome p450scc to biologically active 17alpha,24-dihydroxyergosterol. Chem Biol 2005; 12:931-9.

61. Zbytek B, Janjetovic Z, Tuckey RC, Zmijewski MA, Sweatman TW, Jones E, et al. 20-Hydroxyvitamin D3, a product of vitamin D3 hydroxylation by cytochrome P450scc, stimulates keratinocyte differentiation. J Invest Dermatol 2008; 128:2271-80.
62. Janjetovic Z, Zmijewski MA, Tuckey RC, DeLeon DA, Nguyen MN, Pfeffer LM, et al. 20-Hydroxycholecalciferol, product of vitamin D3 hydroxylation by P450scc, decreases NFkappaB activity by increasing IkappaB alpha levels in human keratinocytes. PLoS One 2009; 4:5988.
63. Slominski AT, Janjetovic Z, Fuller BE, Zmijewski MA, Tuckey RC, Nguyen MN, et al. Products of Vitamin D3 or 7-Dehydrocholesterol Metabolism by Cytochrome P450scc Show Anti-leukemia Effects, Having Low or Absent Calcemic Activity. PLoS One 2010; 5:9907.
64. Zmijewski MA, Li W, Zjawiony JK, Sweatman TW, Chen J, Miller DD, et al. Photo-conversion of two epimers (20R and 20S) of pregna-5,7-diene-3beta, 17alpha, 20-triol and their bioactivity in melanoma cells. Steroids 2009; 74:218-28.
65. Zmijewski MA, Li W, Zjawiony JK, Sweatman TW, Chen J, Miller DD, et al. Synthesis and photo-conversion of androsta- and pregna-5,7-dienes to vitamin D3-like derivatives. Photochem Photobiol Sci 2008; 7:1570-6.
66. Zbytek B, Pfeffer LM, Slominski AT. CRH inhibits NFkappaB signaling in human melanocytes. Peptides 2006; 27:3276-83.
67. 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.
68. Zbytek B, Slominski AT. Corticotropin-releasing hormone induces keratinocyte differentiation in the adult human epidermis. J Cell Physiol 2005; 203:118-26.
69. Zbytek B, Pikula M, Slominski RM, Mysliwski A, Wei E, Wortsman J, et al. Corticotropin-releasing hormone triggers differentiation in HaCaT keratinocytes. Br J Dermatol 2005; 152:474-80.
70. Zbytek B, Pfeffer LM, Slominski AT. Corticotropin-releasing hormone stimulates NFkappaB in human epidermal keratinocytes. J Endocrinol 2004; 181:1-7.
71. Zbytek B, Pfeffer LM, Slominski AT. Corticotropin-releasing hormone inhibits nuclear factor kappaB pathway in human HaCaT keratinocytes. J Invest Dermatol 2003; 121:1496-9.
72. 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.
73. 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.
74. O'Kane M, Murphy EP, Kirby B. The role of corticotropin-releasing hormone in immune-mediated cutaneous inflammatory disease. Exp Dermatol 2006; 15:143-53.
75. Zmijewski MA, Slominski AT. Emerging role of alternative splicing of CRF1 receptor in CRF signaling. Acta Biochim Pol 2010; 57:1-13.
76. Pisarchik A, Slominski AT. Alternative splicing of CRH-R1 receptors in human and mouse skin: identification of new variants and their differential expression. Faseb J 2001; 15:2754-6.
77. Pisarchik A, Slominski A. Corticotropin releasing factor receptor type 1: molecular cloning and investigation of alternative splicing in the hamster skin. J Invest Dermatol 2002; 118:1065-72.
78. Pisarchik A, Slominski A. Molecular and functional characterization of novel CRFR1 isoforms from the skin. Eur J Biochem 2004; 271:2821-30.
79. Zmijewski MA, Slominski AT. Modulation of CRF singaling throught receptor splicing in mouse AtT-20 pituitary cells—Emerging role of soluble isofroms. Journal Physiology and Pharmacology 2009; 60:39-46.
80. Zmijewski MA, Slominski AT. CRF1 receptor splicing in epidermal keratinocytes: potential biological role and environmental regulations. J Cell Physiol 2009; 218:593-602.
81. Slominski AT, Zmijewski MA, Pisarchik A, Wortsman J. Molecular cloning and initial characterization of African green monkey (*Cercopithecus aethiops*) corticotropin releasing factor receptor type 1 (CRF1) from COS-7 cells. Gene 2007; 389:154-62.
82. Bubenik GA. Gastrointestinal melatonin: localization, function and clinical relevance. Dig Dis Sci 2002; 47:2336-48.
83. Zmijewski MA, Sweatman TW, Slominski AT. The melatonin-producing system is fully functional in retinal pigment epithelium (ARPE-19). Mol Cell Endocrinol 2009; 307:211-6.
84. Slominski A, Baker J, Rosano TG, Guisti LW, Ermak G, Grande M, et al. Metabolism of serotonin to N-acetylserotonin, melatonin and 5-methoxytryptamine in hamster skin culture. J Biol Chem 1996; 271:12281-6.
85. Slominski A, Pisarchik A, Johansson O, Jing C, Semak I, Slugocki G, et al. Tryptophan hydroxylase (TPH) expression in human skin cells. Biochim Biophys Acta 2003; 1639:80-6.
86. Zhang X, Beaulieu JM, Sotnikova TD, Gainetdinov RR, Caron MG. Tryptophan hydroxylase-2 controls brain serotonin synthesis. Science 2004; 305:217.
87. Schallreuter KU, Schulz-Douglas V, Bunz A, Beazley W, Korner C. Pteridines in the control of pigmentation. J Invest Dermatol 1997; 109:31-5.
88. Gaudet SJ, Slominski A, Etminan M, Pruski D, Paus R, Namboordiri MAA. Identification and characterization of two isozymic forms of arylamine N-acetyltransferase in Syrian hamster skin. J Invest Dermatol 1993; 101:660-5.
89. Semak I, Korik E, Naumova M, Wortsman J, Slominski A. Serotonin metabolism in rat skin: characterization by liquid chromatography-mass spectrometry. Arch Biochem Biophys 2004; 421:61-6.
90. Roseboom PH, Namboodiri MA, Zimonjic DB, Popescu NC, Rodriguez IR, Gastel JA, et al. Natural melatonin 'knockdown' in C57BL/6J mice: rare mechanism truncates serotonin N-acetyltransferase. Brain Res Mol Brain Res 1998; 63:189-97.
91. Fischer TW, Sweatman TW, Semak I, Sayre RM, Wortsman J, Slominski A. Constitutive and UV-induced metabolism of melatonin in keratinocytes and cell-free systems. Faseb J 2006; 20:1564-6.
92. Slominski A, Semak I, Pisarchik A, Sweatman T, Szczesniewski A, Wortsman J. Conversion of L-tryptophan to serotonin and melatonin in human melanoma cells. FEBS Lett 2002; 511:102-6.
93. Slominski A, Pisarchik A, Wortsman J. Expression of genes coding melatonin and serotonin receptors in rodent skin. Biochim Biophys Acta 2004; 1680:67-70.
94. Kobayashi H, Kromminga A, Dunlop TW, Tychsen B, Conrad F, Suzuki N, et al. A role of melatonin in neuroectodermal-mesodermal interactions: the hair follicle synthesizes melatonin and expresses functional melatonin receptors. Faseb J 2005; 19:1710-2.
95. Fischer TW, Zmijewski MA, Zbytek B, Sweatman TW, Slominski RM, Wortsman J, et al. Oncostatic effects of the indole melatonin and expression of its cytosolic and nuclear receptors in cultured human melanoma cell lines. Int J Oncol 2006; 29:665-72.
96. Slominski A, Chassalevris N, Mazurkiewicz J, Maurer M, Paus R. Murine skin as a target for melatonin bioregulation. Exp Dermatol 1994; 3:45-50.
97. Slominski A, Wortsman J, Plonka PM, Schallreuter KU, Paus R, Tobin DJ. Hair follicle pigmentation. J Invest Dermatol 2005; 124:13-21.
98. Slominski A, Pruski D. Melatonin inhibits proliferation and melanogenesis in rodent melanoma cells. Exp Cell Res 1993; 206:189-294.
99. Fischer TW, Zmijewski MA, Wortsman J, Slominski A. Melatonin maintains mitochondrial membrane potential and attenuates activation of initiator (casp-9) and effector caspases (casp-3/casp-7) and PARP in UVR-exposed HaCaT keratinocytes. J Pineal Res 2008; 44:397-407.
100. Fischer TW, Zbytek B, Sayre RM, Apostolov EO, Basnakian AG, Sweatman TW, et al. Melatonin increases survival of HaCaT keratinocytes by suppressing UV-induced apoptosis. J Pineal Res 2006; 40:18-26.
101. Arck PC, Slominski A, Theoharides TC, Peters EM, Paus R. Neuroimmunology of stress: skin takes center stage. J Invest Dermatol 2006; 126:1697-704.
102. Slominski A, Zmijewski MA, Zbytek B, Brozyna A, Granese J, Pisarchik A, et al. Regulated proenkephalin expression in human skin and cultured skin cells. J Invest Dermatol 2010; In press.
103. Slominski A, Paus R. Melanogenesis is coupled to murine anagen: Toward new concepts for the role of melanocytes and the regulation of melanogenesis in hair growth. J Invest Dermatol 1993; 101:90-7.
104. Slominski A, Paus R, Schadendorf D. Melanocytes as "sensory" and regulatory cells in the epidermis. J Theor Biol 1993; 164:103-20.
105. Slominski A, Paus R. Towards defining receptors for L-tyrosine and L-dopa. Mol Cell Endocrinol 1994; 99:7-11.
106. Slominski A, Paus R. Are L-tyrosine and L-dopa hormone-like bioregulators? J Theor Biol 1990; 143:123-38.
107. 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.
108. Theoharides TC, Cochrane DE. Critical role of mast cells in inflammatory diseases and the effect of acute stress. J Neuroimmunol 2004; 146:1-12.