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Skin as an endocrine organ: implications for its function

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Abstract

Described as the body's largest organ, the skin is strategically located at the interface with the external environment where it has evolved to detect, integrate and respond to a diverse range of stressors. A flurry of recent findings has established the skin as an important peripheral (neuro)endocrine organ that is tightly networked to central stress axes. This capability is contributing to the maintenance of body homeostasis, and in this way could be harnessed for therapeutic strategies.

Introduction

Skin function is a crucial component of organismal survival [1,2]. The skin acts as physical barrier separating the biological milieu from the environment [1], a function that requires precise calibration of cutaneous responses, and a high degree of local autonomy [2]. To that end, it has developed sophisticated sensory, computing and signaling systems to differentially respond to environmental changes represented by biological, chemical, physical or electromagnetic (wide spectrum of wavelengths of solar radiation) factors, and to signal to distant, extracutaneous cells and organs in the mammalian body. The corresponding cutaneous responses are addressed at protecting, restoring or maintaining the optimal body homeostasis [2]. These highly localized responses are coordinated partly by a skin neuroendocrine system that is able to reset adaptation mechanisms through rapid (neural) or slow (humoral) pathways acting at local or systemic levels [2–4].

At the systemic level, the main central regulator of responses to perceived stress is the hypothalamic–pituitary–adrenal (HPA) axis, where activation follows a sequential pattern starting from the release of corticotropin releasing factor (CRF), and involving CRF receptor 1 (CRF1), pro-opio-melanocortin (POMC) and adrenal glucocorticoids synthesis/release; the axis is also modulated by cytokines [5,6]. The same axis is also expressed in the skin, where it represents an important component of the local response to cutaneous stress [4,7].

Effect of psychological stress (PS) on skin (Fig. 1)

PS has been associated with exacerbation and propagation of cutaneous disorders such as psoriasis, atopic dermatitis, delayed wound healing, and risks of infections or recurrence of HSV and H. Zoster [8]. Skin disorders adversely affected by PS are frequently characterized by defective cutaneous permeability barrier function. The potential importance of barrier function is supported by the discovery that atopic dermatitis may be caused by mutations in the filaggrin gene allowing sustained antigen ingress, eliciting a characteristic TH2 immune response [9].

Recent studies have shown that PS compromises permeability barrier function in rodents and humans [10–13]. PS decreases epidermal proliferation and the expression of differentiation markers, such as involucrin, loricrin, and filaggrin, leading to a thin epidermis, and defective corneocytes [14]. PS also reduces the density and secretion of lamellar bodies (LBs) impairing barrier function [14]. PS reduces epidermal cholesterol, fatty acid, and ceramide synthesis and the topical application of lipids restores barrier recovery kinetics to normal in PS animals [14].

Adhesion between adjacent corneocytes is facilitated by corneodesmosomes (CD) (specialized desmosomes of the SC), which rivet together adjacent cells, and by extracellular lipids. Detachment of adjacent corneocytes begins with the progressive, proteolytic degradation of the e-cadherins, DSG1 and DSC1, as well as a unique CD-coating protein, corneodesmosin in the lower SC (stratum compactum). This process is impaired by PS (decreased stratum corneum integrity and cohesion) [14]. Topical applications of exogenous lipids also normalize stratum corneum integrity in PS mice [14].

Systemic and topical GC treatment produce abnormalities in epidermal structure and function in mice virtually identical to those observed in PS [15]. GC decrease epidermal proliferation and differentiation (epidermal thinning or atrophy) and impair permeability barrier homeostasis and SC integrity and cohesion [15]. Similar to PS, GC treatment decreases epidermal lipid synthesis, reduces LB formation, extracellular lamellar membranes and density of CD in SC [15]. Conversely, as in PS animals, topical application of a mixture of barrier lipids largely corrects the GC-induced abnormality in permeability barrier homeostasis and the abnormal SC integrity and cohesion but did not correct the abnormality in either keratinocyte proliferation or differentiation [15]. Thus, GC could mediate the abnormalities in epidermal function produced by PS.

PS stimulates the HPA axis activity with an increase in secretion of the hypothalamic hormone, CRF leading to increased ACTH secretion and adrenal GC production [5,6]. Both inhibition of GC action with RU-486 or pharmacological inhibition of CRF1 with antalarmin prevented the development of PS-induced abnormalities in epidermal structure and function in the face of ongoing PS [16]. GC inhibition restores epidermal lipid synthesis and LB formation/secretion, as well as the density of CD in PS animals, supporting GC as the mediator for the PS-induced abnormalities [16].

The barrier to pathogenic microbes is composed of surface-deposited free fatty acids and AMPs, as well as an intact (cohesive) structurally normal SC [17]. Additionally, the low water content of the intact SC and SC pH of 5.5 encourages the growth of benign bacteria while inhibiting the growth of pathogens [17]. Additionally, AMPs and amphiphilic lipids, particularly sphingosine and free fatty acids, decrease the growth of microbes [17].

PS modulates epidermal AMP levels by reducing CRAMP and mBD3 (the closest murine homologs of LL-37 and hBD2, respectively) protein levels [18]. PS also reduces the delivery

of AMPs to LB [18]. Moreover, the decrease in CRAMP is because of a decrease in gene transcription while the decrease in mBD3 is due to post-translational effects [18].

Systemic or topical GC also decreases CRAMP and mBD3 protein levels in the epidermis [18]. Endogenous GC are probably to account for the PS-induced decline in AMP levels. In the face of ongoing PS, treatment with inhibitors of GC production or action normalizes epidermal protein levels for both CRAMP and mBD3 [18]. Furthermore, adrenalectomy increases the constitutive expression of both AMPs [18].

Co-administration of a mixture of ceramides, cholesterol, and free fatty acids, at a ratio designed to correct the PS/GC-induced inhibition of epidermal lipid synthesis also normalizes mBD3 in PS [18]. The ability of topical lipids to correct the decrease in mBD3 is consistent with post-transcriptional regulation of this AMP by PS/GC.

PS increases susceptibility to cutaneous infections in a GC-dependent fashion [18]. Similar to CRAMP knock-out mice, PS increases susceptibility to group A streptococcus skin (GAS) infections, consistent with the reduction of CRAMP levels [18]. Thus, PS has negative consequences for resistance to cutaneous GAS infections, presumably owing to reduced CRAMP and mBD3 expression.

In conclusion, PS, acting via GC, inhibits keratinocyte proliferation, impairs SC integrity and permeability barrier homeostasis, and decreases SC AMPs increasing the severity of infections (Fig. 1). Such changes could help explain the adverse effects of PS on cutaneous disorders.

Cutaneous expression of CRF signaling system

Human skin expresses the genes for CRF, urocortins 1–2 (URC1, URC2) and produces the corresponding peptides as documented by RP-HPLC, mass spectrometry (MS) and immunocytochemistry analyses [19,20]. In human skin or hair follicles (*in situ*) and/or in cultured human skin cells, the expression of the CRF and production of CRF are stimulated by ultraviolet (UV) radiation and forskolin, and are inhibited by dexamethasone and cortisol [19–21]. Mouse skin also contains fluctuating amounts of CRF peptide (whose concentration actually changes in a hair cycle-dependent fashion), while corresponding CRF transcripts have not yet been documented *in situ*, suggesting that murine skin CRF may arise from an extracutaneous source, for example, local nerve endings [20,22]. Also in mice URC1 production is hair cycle-dependent, albeit in a pattern opposite to that of CRF, whereas URC2 mRNA was detected in the epidermal and dermal compartments of the skin of humans and rodents [19,23]. Cutaneous production of CRF and urocortins appears to be highly compartmentalized, and given the diverse phenotypic effects of the peptides, mechanisms to achieve selectivity in the activation of distinct signal transduction pathways are probably to be operative [19,20].

One such mechanism may result from species- and cell type-specificity in the intracutaneous expression of functional CRF1 and CRF2 [19,23], and/or by alternative splicing of the corresponding transcripts [19,24]. Indeed, selectivity for pleiotropic effects of CRF or URC can be modulated by differential expression of the CRF1 isoforms, particularly the membrane bound and soluble variants [19,23,25]. In human skin, there appears to be exclusive expression of CRF1 in the epidermis with CRF1 α being the most prevalent isoform; CRF2 is only expressed in hair follicle keratinocytes and papilla fibroblasts, sebaceous and eccrine glands, muscle and dermal blood vessels [23]. In mouse skin, both CRF1 and CRF2 are widely expressed in all cutaneous compartments [23].

In cultured human keratinocytes (normal and immortalized) CRF- and URC1-inhibited cell proliferation, while stimulating keratinocyte cell differentiation [19,26]; they also modulate

expression of cell surface adhesion molecules and induce or inhibit cytokines production [19,27,28]. CRF1 and CRF2 are also expressed on sebaceous glands where CRF can stimulate steroidogenic and secretory activities of sebocytes [29]. CRF can also regulate skin function via activation of mast cells expressing CRF receptors [30,31], and participate in the regulation of hair follicle growth and pigmentation [19,32]. These phenotypic effects are mediated by intracellular concentrations of cAMP, IP3, Ca or NF-kappaB activity [19,33]. Overall, the additional non-endocrine-related actions of CRF and related peptides define these peptides as growth factors/pleiotropic cytokines that are capable of regulating proliferation, apoptosis, differentiation, and immune interactions *in vivo* [19,33].

CRF regulates cutaneous POMC expression and production of POMC peptides

Human and rodent skin do express POMC gene and its protein, and further process it to final POMC peptides that include β -LPH, ACTH, α -MSH and β -endorphin [7]. Production and release of these peptides and the POMC precursor occur in cultured skin cells, skin tissue and hair follicle [7]. Of note, at least in mouse skin the POMC gene is alternatively spliced with production of truncated forms [34], also the skin contains the full machinery necessary for POMC processing (PC1, PC2 convertase, and 7B2 protein) [35,36].

POMC peptides interact with MC1, MC2, MC5 and opiate receptors to regulate skin and hair pigmentation, adnexal function, skin immune activity, keratinocytes and fibroblasts activities including those related to differentiation, proliferation and secretory responses [7,36–39]. Although MC2 gene is also expressed in the skin its role in phenotypic actions awaits elucidation [34,40]. There is evidence that the UVB-induced melanogenesis can at least partially be mediated by the upregulation of MC receptors [41,42]. UVR is extremely important determinant of the expression of POMC and production of its peptides and receptors [7,41–43]. In mice expression of MCR1 is hair cycle dependent, highest expression during anagen and the lowest during telogen and catagen, while MC2R expression is constant through the cycle [34].

In epidermal melanocytes, dermal fibroblasts, and hair follicles *ex vivo* CRF stimulates POMC gene transcription and translation with production of ACTH via cAMP-dependent pathway(s) [21,44,45]. The time and dose dependence of this stimulation required activation of CRF1 and was cell type specific. CRF also stimulates α -MSH production and extracellular release of MSH and its POMC precursor, which also act as regulators of melanocyte differentiation program [46]. Interestingly glucocorticoids and some growth factors can inhibit CRF and/or POMC expression in human and mouse skin [19,21,34,36], while POMC expression in murine skin is coupled to the elusive biological clock mechanism regulating hair cycling [34,47].

Cutaneous steroidogenesis

Mammalian skin expresses steroidogenically functional CYP11A1 system [48,49]. Skin cells also express alternatively spliced isoforms of CYP11A1 and cholesterol transport protein MLN64 [48]. Moreover, isolated mitochondria from skin cells can transform cholesterol to pregnenolone and progesterone, though with low efficiency, whereas 22R-hydroxycholesterol is transformed to pregnenolone [48] or 17OH-pregnenolone in cultured skin cells [49].

The genes involved in the sequential metabolism of pregnenolone to corticosteroids, including 3 β HSD, cytochromes P450c17, and P450c21 gene are also expressed in the skin [4,40,49]. Functional activity for these enzymes has been clearly demonstrated in cell extracts and cultured skin cells. Thus, rapid metabolism of progesterone and deoxycorticosterone (DOC) has been shown in rat skin, melanoma cells and immortalized HaCaT keratinocytes [50–52],

whereas in cultured melanoma cells progesterone is sequentially converted to DOC and further to 18OHDOC and corticosterone but not aldosterone [50]. HaCaT keratinocytes rapidly metabolize progesterone and DOC but to products different from corticosterone, aldosterone and cortisol [52]. Cortisol production has been shown in human hair follicle [21], while production of corticosterone and cortisol in cultured normal melanocytes and fibroblasts [4, 44,45,53]. Therefore, the adrenocortical steroidogenic pathway appears to be fully expressed in human skin at the cellular level raising the possibility of intra-, auto or paracrine modes of action [4].

Of further significance is the capability of the cytochrome P450_{scc} to efficiently use substrates other than cholesterol, such as 7-DHC, ergosterol, and vitamins D₂ and D₃ to produce steroidal 5, 7-dienes or hydroxyderivatives of vitamin D or ergosterol [48,54–57]. Lastly, local expression of P450_{scc} in the skin could explain the epidermal accumulation of 22OH-cholesterol, which possibly may play a role in the cutaneous barrier.

Cutaneous HPA axis (Fig. 2)

The expression in the skin of molecular elements of the HPA axis (POMC, CRF, CRF1 and steroidogenic activity including cortisol production) clearly indicates biological significance [2,4,7,19]. Expression of these elements is organized into functional, cell type-specific regulatory loops with a structural hierarchy similar to that found in the central HPA axis [4]. Indeed, the melanocytes respond to CRF with enhanced production of cortisol and corticosterone depending on POMC activity and cortisol production is also stimulated by ACTH or raises in cAMP levels [45]. Dermal fibroblasts respond to CRF and ACTH with enhanced production of corticosterone only [44]; though cortisol is produced constitutively in these cells [53]. In *ex vivo* cultures of human hair follicles CRF or ACTH stimulates cortisol accumulation in keratinocytes of the outer root sheath of the human scalp hair follicle, and secretion into the media [21]. Most interestingly, hydrocortisone treatment of isolated hair follicles is associated with down-regulation of CRF1 in the hair follicle outer root sheath, mirroring the central feedback control of the HPA axis ([21]; Fig. 2).

These observations suggest CRF-driven responses differentially separated to defined stresses affecting cutaneous cell populations or tissue compartments [4,19]. These properties are displayed most clearly by neural crest-derived melanocytes and hair follicles, whose activation sequences and regulatory loops closely reproduce the basic features of the central HPA axis (Fig. 2).

Box 1. Related articles on CRF receptors antagonist/agonists

1. Gulyas, J. *et al.* (1995) Potent, structurally constrained agonists and competitive antagonists of corticotropin-releasing factor. *Proc. Natl. Acad. Sci. U. S. A.* 92, 10575–10579
2. Lewis, K. *et al.* (2001) Identification of urocortin III, an additional member of the corticotropin-releasing factor (CRF) family with high affinity for the CRF2 receptor. *Proc. Natl. Acad. Sci. U. S. A.* 98, 7570–7575
3. Reyes, T.M. *et al.* (2001) Urocortin II: a member of the corticotropin-releasing factor (CRF) neuropeptide family that is selectively bound by type 2 CRF receptors. *Proc. Natl. Acad. Sci. U. S. A.* 98, 2843–2848
4. Rivier, J. *et al.* (2002) Potent and long-acting corticotropin releasing factor (CRF) receptor 2 selective peptide competitive antagonists. *J. Med. Chem.* 45, 4737–4747

5. Rivier, J. *et al.* (2007) Stressin1-A, a potent corticotropin releasing factor receptor 1 (CRF1)-selective peptide agonist. *J. Med. Chem.* 50, 1668–1674

Summary and conclusions

The complex expression of a local HPA axis in the skin and local steroidogenic/secosteroidogenic activities must serve important cutaneous functions. For example, by modulating physical barrier it would provide protection from the responses to chemical and physical insults, and will build antimicrobial and immune activities as well as organize and coordinate the elaborate set of responses to solar radiation at the local and systemic levels. Thus, deregulation of the above coordinating activities could participate in the pathogenesis of conditions such as malignant and benign hyperproliferations, pigmentary disorders, inflammatory dermatoses and dysfunction of adnexal and vascular structures. Current investigations are actively pursuing the effector functions of CRF1 and 2 agonists and antagonists in the regulation of keratinocyte, melanocyte, sebocyte, fibroblast and immunocytes activities (Box 1). Therapeutic targets for CRF receptors agonists/antagonists include psoriasis, inflammatory disorders, alopecia, vitiligo, acne, rosacea as well as solar keratosis, epidermal cancers and melanoma (Box 1). The recently described function and activity of CRF as a growth factor/pleiotropic cytokine implicates differential expression of isoforms of CRF1, and precise coupling to different signal transduction pathways.

Given the common ectodermal origin shared by brain and epidermis, it is possible that the HPA axis may have originated in the integument with primordial actions of regulating the protective mechanisms released by environmental insults ([58]; Fig. 3). Most important may have been protection against UVR (Fig. 4, Box 2) and antimicrobial barrier functions subjected to regulations and fine-tuning by the primordial HPA, because of the close association of its elements. Under evolutionary pressure, this autoregulatory circuitry may have undergone specialization and separation becoming detached from its point of origin and acquiring new functions and location (i.e. CNS, endocrine glands, immune system), while retaining its cutaneous inhibitory activities through action of cortisol/corticosterone (Fig. 3). In this context, the retained cutaneous HPA may serve as an evolutionary record of the parental system. Systemic consequences of this process could underlie the effects of psychological stress-mediated activation of central HPA axis affecting protective and antimicrobial skin barrier functions [18]. This concept potentially leads to therapeutic implications such as the use of systemic or topical selective receptor antagonists for peptide and steroidal messengers of the HPA axis, topical stimulators of cortisol metabolic inactivation and inhibitors of steroidogenesis.

It is still unclear how cutaneous POMC processing differs from the CNS, particularly in relation to PC1, PC2 and 7B2 expression. This information is critical to elucidate the nature of the activity of secretory products. For example, if ACTH were to predominate, one would expect that its stimulation of cortisol production would prevail [4], and the phenotypic effects would be represented by local immunosuppression. If instead, if it were α -MSH, stimulation of melanin pigmentation should represent the main local phenotypic effect [37].

Box 2. Role of the skin in the regulation of adrenal cortex activity

To understand the mechanism(s) involved in the detection and transformation of UVR spectrum of solar radiation into an organized systemic biological response, we have looked for an analogy with the structure of the HPA axis [59]. Our current hypothesis is that global (entire organism) response to UV originates in the skin and it involves multiple pathways encompassing simultaneously the local production of humoral messages and activation or sensory receptors (Fig. 4). Hence, signals generated by the skin are either delivered by

ascending nerve routes to the brain or by circulation to hypothalamus, pituitary or adrenal gland. Thus, stress (UV) would stimulate production and secretion of glucocorticoids via sequential or alternative modes of action originating in the skin, for example, neural transmission to the brain versus humoral activation of either hypothalamus, pituitary or adrenal cortex. These will depend on the wavelength and dose of solar electromagnetic energy as well as on skin anatomy/histology.

The same would apply to β -endorphin, that not only has pro-melanogenic activity but also participates in nociception; (opioid receptors have been identified in epidermal skin cells and nerve endings) [3,38,39].

As regards the skin steroidogenic activity the pathway generating 5,7-steroidal dienes and their secosteroidogenic products is probably to be expressed in human skin (an important repository of the 7-dehydrocholesterol (7-DHC) [48]. The unsaturated B ring of 7-DHC is, in turn, prone to breakage by UVB photons producing vitamin D₃, and analogous photolytic effects on molecules as 7-dehydropregnenolone and/or its hydroxyderivatives (originating from local synthesis or delivery by the circulation) could generate secosteroidal vitamin D-like (vitDL) products [48]. This concept has implications in therapeutic modalities for skin diseases, and the definition of newer neurohormonal or immunomodulatory activities for steroidal 5,7-dienes and/or their secosteroidal derivatives [48] or new vitamin D₂ and D₃ hydroxyproducts [54, 55,57]. Finally, the stressed skin may modify body homeostasis by stimulation of adrenal cortex (Fig. 4, Box 2).

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Figure 1.

The effect of psychological stress on the barrier and antimicrobial functions of the epidermis [14,16,18].

Figure 2. Establishment of a fully functional peripheral homolog of the HPA axis in organ-cultured human scalp hair follicles, including cortisol synthesis and negative feedback-regulation (courtesy of Drs T. and N. Ito, Hamamatsu, Japan) [4,21].

Figure 3.

Integumental origin of the HPA axis. Reprinted from the Journal of Clinical Investigation with the permission [58].