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On the role of the corticotropin-releasing hormone signalling system in the aetiology of inflammatory skin disorders

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Abstract

Corticotropin-releasing hormone (CRH; previously known as corticotropin-releasing factor) is the central regulator of the hypothalamic-pituitary-adrenal (HPA) axis, which is the main organizer of the body's response to stress.[1–5] Stress induces the hypothalamic production and release of CRH, which then causes the activation of the CRH receptor (CRHR) type 1 (CRHR-1) in the anterior pituitary to stimulate ACTH release, as well as proopiomelanocortin (POMC) expression and processing. [1,2,6] ACTH stimulates the production and secretion of cortisol (humans) or corticosterone (rodents) by the adrenal cortex. These steroids regulate the body's response to counteract effects of the stressor and suppress the HPA through the negative feedback mechanism. CRH/POMC expression can also be activated by the cytokines interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)-α, thus involving the immune system in the central regulation of the HPA axis. [7] In addition, CRH together with related urocortin (URC) peptides regulate behavioural, autonomic, endocrine, reproductive, cardiovascular, gastrointestinal and metabolic functions both on the central and on the peripheral levels, and CRH has immunosuppressive effects via the HPA.[6,8–12] It is also accepted that peripheral CRH and related peptides have predominantly proinflammatory functions, [13,14] and in this way differ from their central immunosuppressive activity.[2] However, recent data also suggest that the peripheral CRH may have dual effects: a direct, short-term proinflammatory function and an indirect, remote anti-inflammatory function.[15–18]

The corticotropin-releasing hormone system in the skin

In this issue of the *BJD* Ganceviciene *et al.*,[19] report that the complete CRH signalling system is overexpressed in acne-involved skin with a preferential involvement of the sebaceous glands. Furthermore, the authors propose that overactivation of this CRH system can play an important aetiological role in the development of acne vulgaris through stimulation of local inflammatory reactions.

This conclusion is in accordance with the published information that CRH and related URCs are widely produced by human skin in cell type- and anatomical region-specific manners (reviewed).[15,20,21] Furthermore, this expression is regulated by environmental stressors that includes ultraviolet radiation and bacterial antigens.[15,22,23] The expression is also modified by intrinsic factors such as glucocorticoids or the phase of the hair cycle (reviewed).[21]

Skin cells of both epidermal and dermal compartments also express the functional CRHRs type 1 and 2 (CRHR-1 and CRHR-2), with CRHR-1 being the predominant (if not the sole) CRHR type detected in human epidermis (keratinocytes and melanocytes).[15,24] However, CRHR-2, in addition to CRHR-1, is expressed in dermal cells including hair follicle keratinocytes, melanocytes and follicular papilla fibroblasts, sebaceous and eccrine glands, muscle and dermal blood vessels.[15,24–27] Both receptors belong to the group II subfamily of G protein-coupled receptors.[6] CRHR-1 binds CHR and URC1 with high affinity but does not bind URC2. CRHR-2 shows preferential activation after binding URC2/3, and also binds CRH although

with lower affinity than CRHR-1. The human *CRHR1* gene encodes 14 exons and can generate at least seven alternatively spliced isoforms, of which CRHR1α is the most important.[6,8,15,28] The *CRHR2* gene contains 15 exons and generates several alternatively spliced isoforms with the major forms represented by CRHR2α, β and γ, and with a possibility of generating additional forms because of multiple promoters with intra-intronic location.[6,21,29,30] Coupling of different CRHR-1/2 isoforms to different signal transduction systems or their functional assignments represents a major challenge in this field, which, however, could provide mechanistic explanations for organ- and cell type-dependent variability of phenotypic responses to the ligand.[6,15,28]

Significance of the cutaneous corticotropin- releasing hormone signalling system

In skin cells, CRH and related peptides exhibit nonendocrine activities regulating cell proliferation, viability, differentiation, secretory and immune activities, thereby defining these peptides as novel important growth factors/pleiotropic cytokines.[15,27,31–35] Interestingly, there is a skin compartment- and cell type-dependent variability of phenotypic responses to CRH or URCs.[15,24,25,31] These are sometimes opposite for different cell types (e.g. keratinocytes vs. fibroblasts) [31] or for the same cell type but at a different location (e.g. epidermal vs. follicular melanocytes).[25,31] These phenotypic effects of CRH and related peptides are secondary to modulation of the intracellular concentrations of cAMP, IP3, Ca^{2+}or NF-κB activity (reviewed).[15] We have proposed that the net effect of this diverse CRH/URC-led signalling system(s) is to regulate protective and homeostatic functions of the skin (Fig. 1).

Regulation of the cutaneous corticotropin- releasing hormone signalling system

In the context of data presented by Ganceviciene *et al.*,[19] it must be noted that in normal keratinocytes CRH has proinflammatory effects, e.g. CRH activates NF-κB (the master regulator of inflammation), and stimulates expression of intercellular adhesion molecule-1, HLA-DR and cytokine production (TNF-α, IL-1β and IL-6 but not IL-10, which is unaffected).[16,34,36,37] Furthermore, lipopolysaccharide (LPS; toll-like receptor-4 agonist) stimulates CRH production, and the LPS-stimulated expression of TNF-α, IL-1β and IL-6 is dependent on the expression of CRHR-1.[22] Thus, CRH and its cognate receptor(s) can serve as local amplifiers of inflammatory responses to bacterial antigens and hence be involved in the pathogenesis of acne or other inflammatory dermatoses. Taking into consideration the abundance of data showing proinflammatory actions of CRH in the skin (reviewed),[14,15,36] one is facing a dilemma: why can the system designed to protect and stabilize play a destructive role by being involved in the aetiology of inflammatory skin disorders?[38]

In my opinion, the CRH/URC amplified proinflammatory state is the result of defects in the attenuating homeostatic elements inhibiting either immune activity or CRH/URC signalling or the immune messengers/pathways activated by it (Fig. 2). For example, CRHR-1 activation stimulates cutaneous POMC gene expression and production of potent immunosuppressive ACTH and α-melanocyte-stimulating hormone (α-MSH),[39–42] as well as enhancing the production of cortisol (F) and corticosterone (B) that is POMC dependent.[32,39,42] This functional algorithm defined *in vitro* has been confirmed by Ito *et al.*[40] in an *ex vivo* organ culture system. POMC-derived ACTH and α-MSH (and possibly β-endorphin), as well as corticosteroids, would inhibit directly the proinflammatory chain reaction activated by CRH. The indirect effects would include an immunosuppressive action of melanogenesis intermediates[43] induced directly by activation of CRHR-1[25] or indirectly by activation of

melanocortin-1 receptor by ACTH/α-MSH,[44] or by action of Th2 cytokines stimulated by α-MSH.[45] Thus, in the skin CRH/URC having direct proinflammatory effects can also stimulate indirectly the production of immunosuppressive molecules, which is dependent on the cellular or network context.

The feedback inhibition of CRH production by F or B is well documented in a number of experimental models.[46] An opposite effect, the stimulation of CRH/URC, can be exerted by proinflammatory cytokines IL-1, IL-6 and TNF-α,[7] or possibly by POMC-derived ACTH, α-MSH or β-endorphin (Fig. 2)[15] (e.g. these peptides activate cAMP and Ca signals, which are crucial for CRH/URC production and release).[8,12,46–48] The effects of POMC peptides or cytokines on the CRHR activity itself is unknown; however, such a possibility does exist (Fig. 2). For example, factors raising intracellular cAMP levels or activating protein kinase C can regulate alternative splicing of the CRHR-1 with predominant production of the main CRHR1α isoform.[28] Furthermore, alternative splicing of CRHR-1 and CRHR-2 can also produce soluble forms that lack transmembrane domains and, therefore, after secretion they can bind and sequester the CRH/URC ligands.[15,28] Thus, the cutaneous CRH signalling system represents a dynamic process, being a subject of tight regulation by its downstream regulatory elements (Fig. 2). This regulation is also dependent on the cellular/network context. For example, in keratinocytes CRH is proinflammatory because of poor coupling of the CRHR-1 to cAMP and its dissociation from the POMC activity.[15,31] In contrast, in melanocytes it is anti-inflammatory, e.g. CRH inhibits NF-κB via POMC activation,[17] increases secretion of immunosuppressive glucocorticoids[32] and stimulates melanogenesis,[26] of which intermediates are immunoinhibitory.[44] In this model, the deregulation of the downstream immunosuppressive circuitry may have catastrophic consequences, as proinflammatory reactions can self-amplify as proposed in Figure 2. The central role of the CRHR-1 in the above model implies usage of selective receptor antagonists[49,50] or alternatively spliced soluble isoforms[15] as adjuvants in the therapy of inflammatory skin disorders.

In conclusion, it is proposed that the inefficient local attenuation of the CRH signalling system and/or defective coupling to the downstream immunosuppressive regulatory mechanisms exacerbate or induce proinflammatory responses leading to inflammatory and/or autoimmune disease processes.

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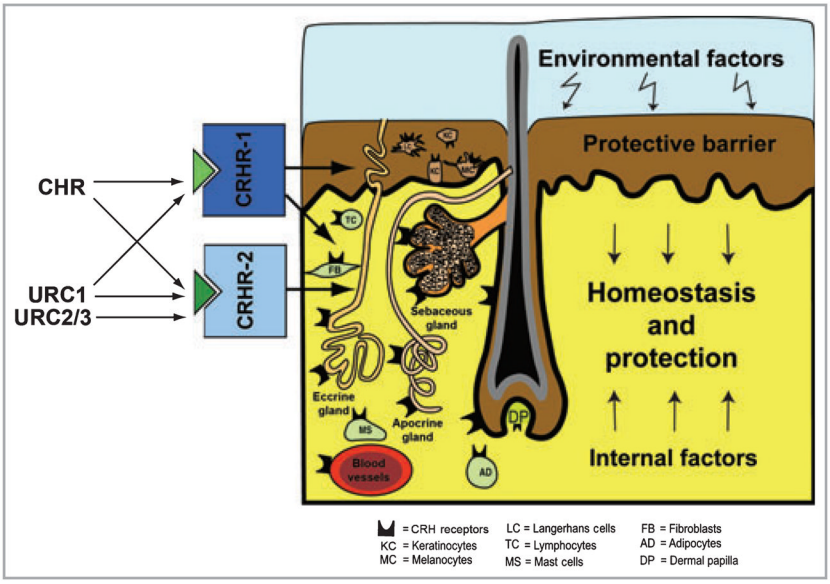

Fig 1.

Corticotropin-releasing hormone (CRH)/urocortin (URC) signalling system regulates protective and homeostatic functions of the skin. CRH receptor (CRHR) type 1 (CRHR-1) is predominantly expressed in the epidermis, while both CRHR-1 and CRHR type 2 (CRHR-2) are expressed in the dermal or adnexal compartments.

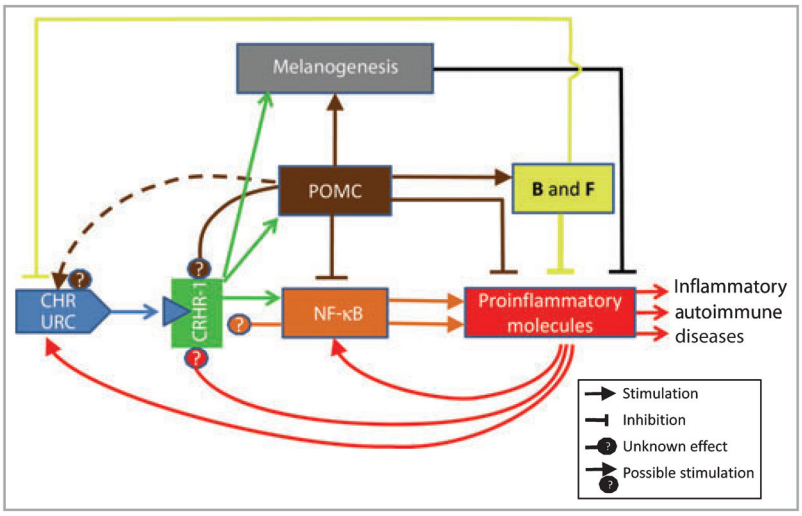

Fig 2.

Dynamic feedback interactions between the immune system of the skin and the local corticotropin-releasing hormone (CRH)/urocortin (URC) signalling cascade. POMC, proopiomelanocortin; B, corticosterone; F, cortisol.