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# Neuroendocrine regulation of sebocytes – a pathogenetic link between stress and acne

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Abstract: A causative link between emotional stress and acne has long been postulated. There is mounting evidence that the molecular mechanism underlying this observation is related to the expression of receptors for several neuroendocrine mediators by the sebaceous gland. Recent and ongoing studies have indicated that human sebocytes express functional receptors for corticotropin-releasing hormone, melanocortins, β-endorphin, vasoactive intestinal polypeptide, neuropeptide Y and calcitonin gene-related peptide. After ligand binding, these receptors modulate the production of inflammatory cytokines, proliferation, differentiation, lipogenesis and androgen metabolism in sebocytes. By means of their autocrine, paracrine and endocrine actions, these neuroendocrine factors appear to mediate centrally and topically induced stress towards the sebaceous gland, ultimately affecting the clinical course of acne.

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## Introduction

The possibility of a causative influence of emotional stress, especially of stressful life events, on the course of acne has long been postulated (1,2). Clinical wisdom and experience (3), as well as many anecdotal observations (4–6) and uncontrolled case series (7), support this opinion. Using a self-administered questionnaire sent to 4000 adult women aged 25–40 years, Poli et al. reported that stress was recorded as the cause of acne in 50% of their patients (7).

However, the role of stressful events in the triggering or exacerbation of acne has not been explored in detail (8). Only one current study met the acceptable methodological standards for stress measurement. Chiu et al., in a prospective study of 22 university students, found that patients with acne may experience a worsening of their disease during examinations (9). Changes in acne severity correlated highly with increasing stress, suggesting that emotional stress from external sources may have a significant influence on acne.

## Neuropeptides and acne

Ongoing research is modifying the classical view of acne pathogenesis through the identification of upstream mechanisms leading to the characteristic clinical lesions, the comedones, followed by follicular inflammation. A hereditary background, androgens, skin lipids, inflammatory signaling and regulatory neuropeptides seem to be mainly involved in this multifactorial process (10). Communication and reciprocal regulation between nervous, endocrine and immune systems are essential for biological stability and responses to external and internal challenges

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(11). In particular, neuropeptides, hormones and cytokines act as signaling molecules that mediate communication between the three interacting systems. In analogy with central responses to stress, which involve predominantly the hypothalamic–pituitary–adrenal (HPA) axis, it has recently been proposed that the skin may share similar mediators (Fig. 1) (12–14). Neuropeptides, originally described in central nervous tissue (15), are also expressed in the skin, in which they exhibit a number of immunomodulatory influences on cellular differentiation (16–20).

## Corticotropin-releasing hormone (CRH) and its relevance for the sebaceous gland

CRH, the most proximal module of the cutaneous HPA-like axis, its binding protein (CRH-BP) and corticotropin receptors (CRH-Rs) act as a central regulatory system of the HPA axis (16,17). Pro-CRH processing into CRH appears to be similar at the central and peripheral levels, including the skin. Current studies have confirmed the presence of a complete CRH/CRH-BP/CRH-R system in human sebocytes. So far, CRH and CRH-R mRNA has been detected in human sebaceous glands by *in situ* hybridization (21). CRH, CRH-BP, CRH-R1 and CRH-R2 are expressed in human sebocytes at the mRNA and protein levels (22). CRH is likely to serve as an important autocrine hormone in sebocytes with a homeostatic pro-differentiation activity. It directly induces lipid synthesis and enhances mRNA expression of Δ5-3β-hydroxysteroid dehydrogenase, the enzyme which converts dehydroepiandrosterone to testosterone in human sebocytes (22,23). Testosterone and growth hormone, which also enhance sebaceous lipid synthesis, have been found to antagonize CRH by down-regulating or modifying CRH-R expression, respectively. On the other hand, CRH enhances keratinocyte immunoactivity by up-regulating the interferon-γ-stimulated expression of homing-associated cell adhesion molecules and intercellular adhesion molecule-1 (ICAM-1) and of the HLA-DR antigen (24). In addition, it enhances interleukin-6 (IL-6) and inhibits IL-1β production in human keratinocytes (25). These findings implicate a major involvement of CRH in the clinical development of seborrhea and acne, as well as in other skin disorders and diseases associated with alterations in the formation of sebaceous lipids.

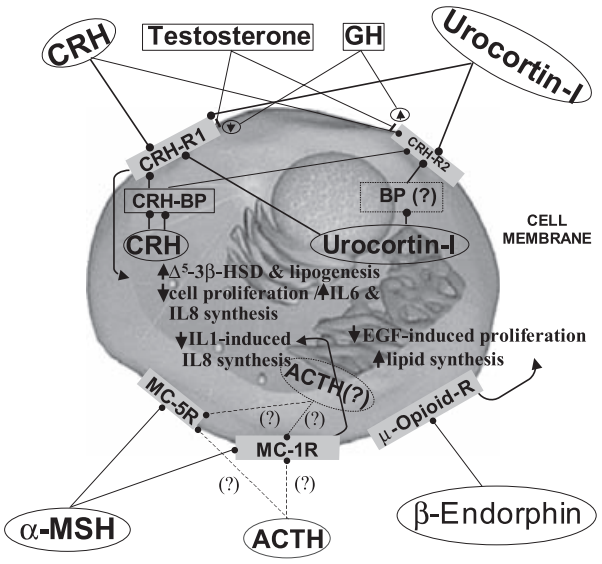


*Figure 1.* The sebocyte hypothalamic–pituitary–adrenal (HPA)-like axis influences sebocyte proliferation, differentiation and activity [data from (21,22,38–42,44–50)]. Δ5-3β-HSD, Δ5-3β-hydroxysteroid dehydrogenase; ACTH, adrenocorticotropin; BP, binding protein; CRH, corticotrophin-releasing hormone; CRH-BP, corticotrophin-releasing hormone binding protein; CRH-R, corticotrophin-releasing hormone receptor; EGF, epidermal growth factor; GH, growth hormone; MC-R, melanocortin receptor; α-MSH, α-melanocyte-stimulating hormone; R, receptor.

## Melanocortins and their putative role in human sebocyte biology

The elucidation of the role of melanocortins, i.e. adrenocorticotropin (ACTH) and α-melanocyte-stimulating hormone (α-MSH), on sebaceous gland activity goes back to the substantial work of Ebling, and Thody and Shuster (26–28). These researchers dissected the *in vivo* effect of several pituitary hormones on sebum production and preputial gland activity in experimental animal models. As adrenalectomy reduces sebum secretion in both intact and castrated rats, and ACTH does not increase it, ACTH appears to act on the sebaceous gland presumably indirectly, i.e. via induction of adrenal androgens (29). It has been demonstrated that removal of the neurointermediate lobe alone decreases sebum secretion to an extent comparable with that after total hypophysectomy (30). As the pars intermedia is a source of α-MSH in rodents, and this neuropeptide increases sebum secretion in both intact and hypophysectomized rats, α-MSH is classified as a pituitary-derived sebotrophic hormone (31). α-MSH synergizes with testosterone as well as progesterone on sebum secretion by an unknown mechanism

(32,33), and specifically affects the biosynthesis of wax esters and sterols in the rat animal model (32). With regard to the early endocrine environment, α-MSH administered *in utero* and, to a lesser extent, during neonatal life permanently enhances sebum secretion (34). However, subsequent studies have failed to establish a direct effect of α-MSH on the sebum rate in adrenalectomized animals for reasons not fully understood (27). Since then, a direct sebotrophic activity of α-MSH has been a matter of debate and, in humans, definitive evidence for such an activity of α-MSH has been missing until recently.

Cloning of the melanocortin receptors (MC-Rs) (35), application of novel research tools and the generation of an immortalized human sebaceous gland cell line (36) have paved the way for novel and ongoing studies aimed at ultimately delineating the action of α-MSH in sebocytes. MC-5R knock-out mice exhibit reduced exocrine gland function (37). The transgenic animals show reduced sebum secretion, lack of Nle (4), D-Phe (7)]α-MSH (NDP-MSH) radiolabeling of the preputial glands and a loss of NDP-MSH-induced cyclic adenosine monophosphate increase in membrane fractions from these glands. MC-5R expression has also been demonstrated in microdissected human facial sebaceous glands, as well as in facial skin biopsy specimens, by immunohistochemistry (38,39). We have been unable to detect MC-5R expression in human sebocytes, but have found MC-1R expression in both human sebaceous glands *in situ* and in the human facial sebaceous gland-derived cell line SZ95 (40). α-MSH *in vitro* inhibited the IL-1β-induced secretion of IL-8, providing the first evidence for a direct activity of α-MSH in human sebocytes (40). MC-1R expression by human sebocytes derived from human facial skin was confirmed by others, who demonstrated that the superpotent α-MSH derivative, NDP-MSH, increased lipogenesis, i.e. squalene synthesis (41). Preliminary data have indicated that natural melanocortins likewise enhance lipogenesis in SZ95 sebocytes, but do not appear to synergize with testosterone (M. Böhm et al., unpublished findings, 2004). Whether α-MSH or additional melanocortins are produced by sebocytes is unclear. RNA expression of the precursor protein, proopiomelanocortin (POMC), was detected by reverse transcriptase-polymerase chain reaction in laser capture microdissected human sebaceous glands (21). On the other hand, SZ95 sebocytes lack RNA and protein expression even following stimulation with prototypical POMC inducers (42,43).

In summary, these findings have established the human sebocyte as a direct cellular target of α-MSH, which appears to regulate lipogenesis and the production of proinflammatory cytokines. Although our current knowledge about the biological effects of melanocortins on the human sebaceous gland is still incomplete, it is expected that, within the next few years, the role of α-MSH will be further clarified with regard to lipid formation, immunomodulation and potential involvement as a player in disorders of the sebaceous gland.

## Endogenous opioids – another class of sebotrophins?

Recent evidence has suggested that β-endorphin (β-ED), another POMC-derived peptide and member of the endogenous opioid family of neuropeptides, has sebotrophic activity. The μ-opioid receptor, which binds β-ED with high affinity, is expressed by the human sebaceous gland *in situ* as well as by SZ95 sebocytes *in vitro* (42,43). Stimulation of SZ95 sebocytes with β-ED in chemically defined medium suppresses the *in vitro* proliferation induced by epidermal growth factor. Most interestingly, β-ED stimulates lipogenesis and specifically increases the amount of C16:0, C16:1, C18:0, C18:1 and C18:2 fatty acids to an extent similar to linoleic acid (43). These data highlight another prototypical stress-induced neuroendocrine mediator that acts on the human sebocyte and modulates proliferation, differentiation and lipogenesis.

## Role of other neuropeptides in the regulation of clinical inflammation in acne

There is current evidence that further neuropeptides with hormonal and non-hormonal activity may control the development of clinical inflammation in acne. Substance P immunoreactive nerve fibers have been detected in close apposition to the sebaceous glands, and expression of the substance P-inactivating enzyme, neutral endopeptidase, has been observed within sebaceous germinative cells of acne patients but not of healthy volunteers (44,45). *In vitro* experiments using an organ culture system demonstrated that substance P induced the expression of neutral endopeptidase within sebaceous germinative cells in a dose-dependent manner. Moreover, a significant increase was detected in the

size of the sebaceous glands and in the number of sebum vacuoles in sebocytes on treatment with substance P (44).

Moreover, nerve growth factor showed immunoreactivity only within the germinative sebocytes (45). An increase in the number of mast cells and a strong expression of endothelial leukocyte adhesion molecule-1 on the post-capillary venules were observed in adjacent areas to the sebaceous glands. Of several molecules produced by mast cells, only IL-6 induced sebocytes to produce nerve growth factor (45). Vasoactive intestinal polypeptide (VIP) receptors (VPAC) were expressed in human sebocytes, with VPAC2 exhibiting the most pronounced expression in cells surrounded by VIP immunoreactive nerve fibers (46). Sebocytes also express neuropeptide Y and calcitonin gene-related peptide receptors (46).

## Outlook

There is increasing evidence to suggest that the nervous system (such as emotional stress) can influence the course of acne. Cutaneous neurogenic factors may contribute to the onset and/or exacerbation of acne inflammation (45). The current findings described here indicate that central (13–15) or topical (16–20) 'stress' may, indeed, influence the feedback regulation in the sebaceous gland, thus inducing the development of clinical inflammation in early acne lesions. The identification of the precise action of such neuromediators on the sebaceous gland can be further expected to offer novel treatment options with 'biologicals' in order to normalize the altered formation of sebaceous lipids in various skin disorders.

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