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Review

Neuroendocrine regulators

Novel trends in sebaceous gland research with future perspectives for the treatment of acne and related disorders

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There is compelling evidence that the sebaceous gland is not only a passive endocrine target organ that reacts to sex hormones with well established responses but also plays an integral and active part of various neuroendocrine/neuromediator axes within the skin. In this review, our current knowledge on the expression, regulation, and function of melanocortin peptides, corticotropin-releasing hormone, endogenous opioids including their receptors, and of other neuromediators, in normal and diseased human sebocytes will be described. Understanding the function of these newly recognized players in sebocyte biology will extend our present pathogenetic concepts of acne and related diseases. Moreover, these newly discovered mediators and their receptors in human sebocytes form a rich basis for the future design of neuroendocrine therapies for patients with sebaceous gland disorders.

Introduction

The idea that the sebaceous gland is a direct target organ for neurohormones, neuro-mediators and/or neurogenic stimuli is a plausible concept.[1,2] Clinical experience and wisdom has long suggested that stress-related neurohormonal factors or mediators could be involved in stress-induced acne.[3,4] However, only recently, scientific evidence has emerged for such a stress-induced impact on acne as demonstrated on university students undergoing examination.[5]

Our current and now widely accepted concept that the skin with its various cellular players is not only a target structure but also a rich autonomous source of many neurohormones[6] further supports the idea of the sebaceous gland as an active player within the cutaneous neuroendocrine network.

In the following sections, the most recent data regarding the expression, regulation and function of such neuroendocrine mediators in human sebocytes in vitro and in situ (i.e. in skin of patients with acne and related disorders) will be summarized. It should be noted that the term "neuroendocrine" was originally reserved for hormones being produced within classical neuroendocrine organs such as the pituitary gland. As the skin with its various cell types can likewise generate such factors,[6] the term "neuroendocrine" may appear somewhat confusing if not historic. However, the terms "neuroendocrine" and" neurohormones" still will be used as umbrella terms in this article to emphasize that virtually all components of the classical neuroendocrine axes are installed within human sebocytes or sebaceous glands.

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Corticotropin-Releasing Hormone (CRH) and CRH Receptors

Although not the first neurohormone identified as a neuroendocrine regulator of sebocytes, CRH is clearly the most upstream player of the classical endocrine hypothalamic-pituitary-adrenal axis (HPA).

Using laser-capture microdissection with RT-PCR, Kono et al. were the first who detected mRNAs of CRH and the CRH receptor (CRH-R) in captured human sebaceous glands in situ.[7] When CRH and CRH-R expression was investigated in human sebocytes growing in vitro, the immortalized sebocyte cell line SZ95 was found to express CRH, CRH-binding protein (CRH-BP) and CRH-R1 and 2 at the mRNA and protein level. CRH-R1 was more abundant than CRH-R in these cells.[8] In accordance with the expression of CRH, CRH-Rs and CRH-BP in SZ95 sebocytes, CRH immunoreactivity was described in sebaceous glands of healthy individuals as well as in those with alopecia areata.[9] Most recently, immunoreactivity of CRH, CRH-R1/2 and CRH-BP was investigated by immunohistochemistry in acne. Very strong positive immune reactions for CRH were seen in acne-involved skin in all types of sebaceous gland cells, irrespective of their differentiation stage. Sebaceous glands in noninvolved and normal skin displayed weaker CRH staining depending on the differentiation stage of the cells. Moreover, the most prominent CRH-BP immunostaining in acne-involved sebaceous glands was seen in differentiating sebocytes.[10]

At the functional level, CRH induces lipidogenesis and increases the expression of 3β-hydroxysteroid dehydrogenase/

Δ^{5-4}-isomerase, an enzyme converting dehydroepiandrosterone to testosterone. Testosterone suppresses CRH-R1 and CRH-R2 mRNA expression in SZ95 sebocytes while growth hormone switches CRH-R1 mRNA expression to CRH-R2.[8] Interestingly, CRH did not modulate IL-1β-induced expression of the proinflammatory cytokine interleukin (IL)-8 in SZ95 sebocytes suggesting that in contrast to α-melanocyte-stimulating hormone (α-MSH)[11] this neurohormone has no anti-inflammatory effects in sebocytes. In fact, further studies revealed that CRH in vitro stimulated the release of both IL-6 and IL-8 by SZ95 sebocytes supporting a proinflammatory role of this peptide.[12] In addition, CRH and the structurally related CRH-like peptide urocortin inhibited SZ95 sebocyte proliferation.[12]

These findings support the previously proposed role of CRH as a master coordinator of the cutaneous stress response as already suggested by A. Slominski.[13] Increased immunoreactivity of CRH within the sebaceous gland, in particular, could indicate that a locoregional "seboglandular" HPA-like stress axis is turned on in patients with acne via CRH. Accordingly, CRH in concert with other cofactors such as androgens may increase lipogenesis and worsen the course of acne.

Future studies will have to clarify the precise roles of CRH and its receptor in the pathogenesis and course of acne. As pointed out above, CRH immunostaining is also stronger in sebaceous glands of patients with alopecia areata. As there is usually no acne-like disease or folliculitis in affected skin of patients with alopecia areata, increased seboglandular CRH expression in these individuals may point towards an unspecific or secondary phenomenon.

Regarding the clinical perspectives of CRH and its receptors in acne and related disorders it should be noted that CRH-R antagonists could possibly emerge as future therapeutics. Interestingly, it has been demonstrated that α-helical-CRF, a CRH antagonistic peptide is capable of annulling the CRH effect on SZ95 sebocyte proliferation and the release of both IL-6 and IL-8 from these cells.[12] Moreover, antalarmin, a non-peptide CRH-R1-specific CRH antagonist, suppressed the CRH-mediated upregulation of neutral lipids in SZ95 sebocytes.[12]

Natural Melanocortins, Melanocortin Receptors (MC-Rs) and Melanocortin Peptide Derivatives

When reviewing the role of natural melanocortins in sebaceous gland biology, credit must be given to the pioneering work A. Thody. This scientist together with his co-workers extensively studied the sebotrophic effects of both α-MSH and adrenocorticotropin (ACTH) on the rat preputial gland in vitro and in vivo. Both natural melanocortin peptides originally characterized as classical neurohormones released from the rat pituitary gland and pars intermedia, respectively, were found to increase sebum secretion in this model.[14,15]

However, only recently, functional effects of α-MSH were identified in human sebocytes. It could be demonstrated that the neuropeptide both in absence and presence of IL-1β dose-dependently inhibits secretion of IL-8, a chemokine crucially involved in the pathogenesis of acne vulgaris.[11] Subsequent studies investigating the effect of ACTH and the superpotent MSH analogue [Nle4, D-Phe7]-α-MSH (NDP-α-MSH) confirmed direct lipogenic effects of these melanocortin peptides, i.e. they increased cytoplasmic lipid droplet formation at a level similar to stimulation with bovine pituitary extract (containing natural melanocortins). In addition, NDP-α-MSH increased squalene synthesis in a dose-dependent manner with peak synthesis of squalene at 10 nM.[16]

The effects of these melanocortin peptides appear to be mediated via MC-Rs. These are small heptahelical surface receptors which belong to the superfamily of G protein-coupled receptors. All so-far cloned MC-R subtypes, MC-1-5R, activate Gs resulting in activation of adenylate cyclase and increase of intracellular cAMP. In human sebocytes, expression of both MC-1Rs and MC-5Rs was detected.[11,16-19] Initial discrepancies regarding the predominance of MC-5R over MC-1R or vice versa in human sebocytes are probably related to technical difficulties with the MC-R detection methodology or due to exclusive use of a particular in vitro model. Accordingly, SZ95 sebocytes, a sebocyte cell line derived from human facial primary sebocytes, appear to have lost MC-5R during the Simian virus-40 large T antigen-mediated immortalization process.

The distribution of MC-1R and MC-5R immunoreactivity was found to be different in human sebaceous glands in situ. MC-5R immunostaining was mainly detected in terminally differentiated cells while MC-1R immunoreactivity was most accentuated in the peripheral, non-differentiated cells of the sebaceous acini.[11,18] It was therefore suggested that MC-5R is involved in terminal differentiation of sebocytes. In accordance with this hypothesis, MC-5R mRNA expression was only detected in primary human sebocytes at the onset of differentiation and in fully differentiated cells containing lipid granules.[18] In a recent study of 33 patients with acne vulgaris and seven age-matched volunteers, MC-1R expression was further investigated by immunohistochemistry.[20] Sebocytes and keratinocytes of the ductus seboglandularis of acne-involved and non-involved skin showed very intense MC-1R expression in contrast to less intense scattered immunoreactivity in normal skin samples. These findings point towards a role of the MC-1R in the pathogenesis of acne. One possibility is that MC-1R overexpression in sebaceous glands of acne patients is induced by seboglandular stress, perhaps by the most upstream stress coordinator CRH. Other stressors, especially IL-1, may likewise increase MC-1R expression in the context of the inflammatory process of the pilosebaceous during acne. It needs to be shown whether increased expression of MC-1R in sebocytes in acne vulgaris is a common epiphenomenon in other skin diseases in which no aberrant function of the sebaceous glands exist.

In light of the well-documented role of α-MSH and its receptor MC-1R in the context of immunomodulation,[21] it is possible that the MC-1R expressed by human sebocytes is more involved in immunoregulation than MC-5R. The latter may be more concerned with lipogenesis in sebocytes. Of note, transgenic mice with targeted disruption of MC-5R displayed reduced sebum secretion, lack of NDP-MSH radiolabelling of the preputial glands and loss of NDP-MSH-induced cAMP increase in membrane fractions from these glands.[22] In situ expression of MC-5R could be

demonstrated in secretory epithelia in both the preputial gland as well as sebaceous glands in the skin of normal mice. However, we still do not know whether mice with targeted disruption or signal deficiency of MC-1R display impaired sebum production.

Whether human sebocytes in vitro or in vivo autonomously generate melanocortins is incompletely investigated. Artificial cAMP inducers such as forskolin and choleratoxin were found to induce POMC mRNA expression in primary human facial sebocytes according to preliminary data.[23] POMC mRNA has also been detected by RT-PCR in laser capture microdissected human sebaceous glands.[7] More recently, immunostaining of both α-MSH and ACTH was found in hair follicle epithelia and in secretory epithelia of sebaceous glands in patients with alopecia areata and control patients.[24] Immunostaining of α-MSH in the sebaceous glands was more accentuated in lesional skin of patients with alopecia areata suggesting induction of the cutaneous HPA axis by disease stress.

Regarding a translational research approach on MC-Rs in human sebocytes, the situation appears to be complex for the treatment of patients with acne vulgaris and related disorders. Given the proposed role of MC-5R as a pro-differentiating and sebotrophic receptor, antagonism of the MC-5R may be a novel therapeutic strategy in patients with acne. Clinical trials with a novel MC-5R antagonist have been initiated in patients with acne vulgaris (Johnson & Johnson, personal communication).

An alternative new strategy may be the use of truncated MSH peptides/derivatives not containing the central pharmacophor (amino acids 6–9 of α-MSH) which mediates the melanotropic effect of natural melanocortins.[21] Such truncated small peptides are the tripeptides KPV [α-MSH (11-13)] and the α-MSH derivative KdPT, the latter exhibiting potent in vitro and in vivo anti-inflammatory effects (Mastrofrancesco & Böhm, submitted).

Endogenous Opioids and Their Receptors

Another group of POMC-derived neuropeptides in addition to the melanocortins are the endogenous opioids. Among them, especially β-endorphin (β-ED) has attracted most attention as a prototypical stress-responsive neurohormone. In fact, several proinflammatory conditions of the skin such as psoriasis, scleroderma and atopic eczema exhibit increased peripheral blood levels of this neuropeptide.[25] Preliminary data from our laboratory also indicate that patients with severe acne vulgaris, hidradenitis suppurativa, and acne conglobata have also increased plasma levels of β-ED (Böhm et al., manuscript in preparation). However, there is currently no evidence that β-ED is produced in the human sebaceous gland itself.[26] This is in contrast to several rodent species, e.g. in the mouse in which β-ED is expressed in a hair follicle cycle-dependent manner in the pilosebaceous unit.[27]

Recently, we have addressed the possible role of β-ED as a modulator of sebocyte function in sebocytes in vitro (Böhm et al., manuscript in preparation). Treatment of SZ95 sebocytes with β-ED induced cytoplasmic lipid droplet formation and suppressed cell proliferation induced by epidermal growth factor. These findings suggested a pro-differentiating effect of β-ED in sebocyte biology. More detailed lipid analysis revealed that β-ED specifically increased the amount of various fatty acids but not of squalene like melanocortin peptides. In order to elucidate the mechanism of this effect of β-ED in human sebocytes, expression analysis of the μ-opioid receptor (MOR) and δ-OR (DOR), both of which bind β-ED with high affinity, were studied. RT-PCR analysis, western immunoblotting and immunocytochemical studies disclosed the presence of the MOR in both SZ95 sebocytes as well as in the human sebaceous gland of healthy volunteers while DOR was undetectable.

The above data add another player to the growing list of neuroendocrine mediators influencing sebocyte function. The action of β-ED in human sebocytes suggests a role of this peptide as a novel "sebotrophin" with possible implication in the pathogenesis of acne and related disorders. Currently, the expression of MORs in the skin of patients with acne is under investigation in our laboratory. The idea behind is that the MOR expressed by sebocytes could become a novel molecular target for acne treatment, e.g. by using MOR antagonistic agents. On the other hand, MOR agonists could be useful for the future treatment of dry skin.

Other Neuroendocrine Mediators

A number of reports indicate that human sebocytes are also integrated in so-called neurogenic stress axes. Neurogenic neuromediators are classically released by nerve fibers and exert pro-inflammatory responses on cells of the immune system and/or on resident cells of many peripheral tissues including the skin.[28,29]

A prototypical mediator of neurogenic inflammation is substance P (SP). It was shown that SP can alter the morphology and ultrastructure of sebaceous glands in skin organ cultures.[30] SP promoted the development of cytoplasmic organelles, stimulated sebaceous germinative cells, and increased the size of the sebaceous glands. More recently, it was reported that SP in primary human sebocytes increases the mRNA expression levels of IL-6, IL-8, TNF-α and peroxisome proliferators activated receptor-γ, the latter a nuclear hormone receptor involved in lipogenesis.[31] These effects of SP were associated with increased immunoreactivity of the above molecules. Since the number of SP-containing nerve fibers around sebaceous glands appear to be increased in acne patients compared to healthy subjects[32] these findings would suggest a pathogenic role of SP as a potential mediator of neurogenic inflammation in acne.[33] It will be highly interesting to prove the proposed role of SP in acne by treating acne patients with SP antagonists such as apprepitant.

Another well established player in neurogenic inflammation is nerve growth factor (NGF). Immunoreactivity for NGF and its high affinity receptor, tyrosine kinase A (TrkA) was detected in both sebaceous glands of skin from healthy volunteers[34] and in sebaceous glands of skin from acne patients.[33] The concomitant expression of NGF and TrkA by sebocytes would suggest an autocrine or paracrine mode of action of this neuromediator. However, since IL-6 induced NGF expression in sebocytes of human facial organ cultures, this finding was interpreted as a potential mechanism of increased periglandular innervation and possibly neurogenic inflammation in acne vulgaris.[33]

In another study, the neurotransmitter serotonin was detected by immunohistochemistry within the cytoplasm of the sebaceous glands of patients with chronic eczema.[35] The functional role of serotonin in sebaceous glands and sebocytes remains to be determined but it should be noted that most skin cells harbour the full enzymatic capacity to synthesize serotonin.[36]

Two other immunohistochemical studies indicated that human sebaceous glands are targets for somatostatin and for vanilloids. Accordingly, in situ expression of all five somatostatin receptor subtypes was detected in sebaceous glands of normal human skin.[37] So far, the effect of somatostatin on sebocytes however is unknown.

Moreover, the vanilloid receptor subtype 1 (VR1/TRPV1) was detected in both cutaneous sensory nerve fibers and in various resident skin cells including the sebaceous gland. In the sebaceous gland, VR1 immunoreactivity was most accentuated in differentiated sebocytes whereas the undifferentiated cells were largely negative.[38] In accordance with these data it was shown that SZ95 sebocytes likewise express TRPV1. Using the non-selective cation channel vanilloid alkaloid capsaicin it was further demonstrated that this agent selectively inhibits basal and arachidonic acid-induced lipid synthesis in a dose-, time-, and extracellular calcium-dependent and a TRPV1-specific manner. Low-dose capsaicin stimulated SZ95 sebocyte proliferation via TRPV1, whereas higher concentrations inhibited sebocyte growth and induced cell death independent of TRPV1. In addition, capsaicin suppressed the expression of genes involved in lipid homeostasis and of selected proinflammatory cytokines. The above findings introduced a previously unreported player in human sebocyte biology and identified TRPV1 as a new target in the clinical management of inflammatory disorders of the sebaceous gland.[39]

Summary

There is now clear-cut evidence that the human sebaceous gland is both a prominent source and target structure for various neurohormones and neuromediators previously detected only in classical neuroendocrine organs or in nerve fibers. In addition to providing fascinating new insight into the regulation of sebocyte function, these findings will help to explain long-suspected functional interactions between "stress" and the course of acne. Most interesting for the clinician, however, are the highly promising future directions based on the described functional activities of neuromediators in human sebocytes. It is strongly hoped that such neuroendocrine treatment strategies as outlined above will find their way into clinical routine to enrich our daily management of patients with inflammatory disorders of the sebaceous gland.

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