Chapter 4

Neuroendocrine Controls of Keratin Expression in Human Skin

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Abstract

The human skin serves as a source for a large number of neurohormones and neuropeptides, which affect skin biology on multiple different levels. Intriguingly, this includes the control of keratin expression by neurohormones such as thyrotropin-releasing hormone, thyrotropin, opioids, prolactin, and cannabinoid receptor 1-ligands. While this neuroendocrine regulation of human keratin biology *in situ* is likely to be involved in the maintenance of skin and hair follicle homeostasis and may participate in skin pathology, this regulation remains to be appreciated and explored by mainstream keratin research. Here, we review recent progress in this frontier of neuroendocrine and keratin skin research, define the many open questions in the field, and elaborate how neurohormones may be harnessed to treat selected genodermatoses and other skin disorders accompanied by abnormal keratin expression.

Keywords: keratins, neuroendocrinology, hair, skin, dermatology

1. Introduction

Keratins are the major constituents of the epidermis and skin appendages, which by forming an intracellular structural network provide cellular stability and resilience to the tissue [1]. Furthermore, they exert a surprisingly wide and complex range of additional functions in the skin, including regulating epithelial differentiation and proliferation, migration and wound healing, carcinogenesis and apoptosis, and immunomodulation [2–5]. Taking into consideration the key roles keratins play in the skin, it is of utmost importance to understand and dissect the mediators that affect their expression. One of the key mediators of skin function is the endocrine system, which is also expressed and active in the skin itself.

An important pathway by which the endocrine system controls skin function is by changing keratin expression, and these effects have been described in detail previously [6].

Throughout the last decade, it became clear that the skin reacts and generates not only steroid hormones, but also a large array of neuroendocrine mediators [2, 3, 7–10]. The skin has even formed a hypothalamic-pituitary-adrenal (HPA) neuroendocrine signaling axis, equivalent to the central axis [10–12], and a semi-equivalent hypothalamic-pituitary-thyroid (HPT) axis [13–16]. These neuroendocrine mediators take part in the regulation of many different processes and functions of the skin, both in normal healthy skin and in disease states. These include, for example, regulation of stress response [10, 17], hair follicle (HF) growth [18–22], pigmentation of the skin and HF [18–21, 23, 24], sebaceous gland function [10, 12], proliferation and apoptosis of keratinocytes [9, 10, 25], and mitochondrial activity [16, 26, 27]. They are also involved in controlling the immune privilege of the HF epithelium and the immune response of the skin [24, 28].

Taking into consideration the fact that keratins constitute up to 85% of the cell mass of a terminally differentiated keratinocyte and have such important roles not only in keratinocyte, sebocyte, and trichocyte biology, but also for overall skin physiology [29–31] and the fact that the vast majority of neuroendocrine mediators is expressed in the skin epithelium [11, 12, 17], it is reasonable to ask whether some of the functions exerted by neurohormones in the skin are actually mediated by changing keratin expression. Indeed, in recent years, several studies have demonstrated that keratin expression in human skin and HFs is manipulated by neurohormones and underlies previously ignored, important neuroendocrine controls that invite therapeutic targeting.

In this chapter, we systematically explore the effects of neuroendocrine mediators on keratin expression and connect these changes to physiologically relevant functions of the skin and HFs. We also dissect the ways by which such keratin changes might be harnessed to alleviate different skin conditions.

2. The hypothalamic-pituitary-thyroid axis in the skin and its effects on keratin expression

The fact that skin and HFs are prominent targets for the thyroid hormones, triiodothyronine and thyroxine, is well established [15, 16]. These thyroid hormones also promote cutaneous wound healing [32, 33]. Furthermore, patients suffering from thyroid disorders manifest with significant hair and skin phenotypes [15]. It is possible that some of these changes are due to an effect of thyroid hormones on keratin expression. For example, T3 increases K6, K16, and K17 gene expression in human keratinocytes in culture, keratins that are known to be upregulated during the wound healing process [34], and mice with hypothyroidism have reduced K6 expression [34]. In addition, T3 and T4 stimulate K6 expression and decrease K14 expression in cultured human HFs [15].

However, thyroid hormones can themselves change the production of neurohormones such as prolactin and thyroid-stimulating hormone (TSH, thyrotropin), also in the skin [13, 35].

Indeed, in recent years, it has become evident that the skin expresses receptors for the thyroid hormones and for TSH and thyrotropin-releasing hormone (TRH) [13, 18, 23, 26]. It has also been observed that, just as in the central HPT axis, thyroid hormones decrease intraepidermal TSH expression, while TRH stimulates it in human skin, therefore suggesting that an elementary functional HPT axis also exists in the human skin [36].

Thyrotropin-releasing hormone is expressed by the human HF and can be found in the outer root sheath (ORS). The TRH receptor (TRH-R), on the other hand, is expressed in the inner root sheath (IRS) of the HF [23]. TRH can affect keratin expression: it has been found to upregulate the expression of the hair keratins K31 and K32, while it downregulates the expression of the hair keratins K85 and K86 at the protein level [37]. TRH also has profound effect on the keratins expressed by the ORS in the HF, leading to reduced expression of K6, K14, and K17 [23, 37]. The above-listed keratins have been confirmed to be regulated by TRH at the protein level in the HF, but it should be noted that additional keratins and keratin-associated proteins (KAPs) may be affected by TRH according to microarray results obtained with organ-cultured human HFs [37]. However, further experiments are required to confirm regulation of these keratins and KAPs by TRH. Another important open question is to which extent the TRH-induced changes in keratin expression observed in the HF underlie the complex functional changes exerted by TRH in the HF [2, 16], namely, the stimulation of hair shaft production by TRH [23].

In contrast to the ORS of the HF, TRH stimulated K6, K14, and K17 expression in the epidermis, sweat glands, and sebaceous glands in human skin *ex vivo* at the protein and mRNA levels [37]. The same promoting effect of TRH on human K6 expression was also evident in frog skin *in vitro* [25], and this stimulating effect was suggested to accompany the promotion of wound healing in the frog skin [25]. This suggests that the keratin regulatory effects of TRH are highly conserved in vertebrate skin and underscores the functional importance of this neuroendocrine control of keratin biology. This makes it even more surprising that mainstream keratin research continues to largely ignore this evolutionarily conserved control mechanism, which must have provided significant species survival advantages to have been maintained from frogs to humans. Interestingly, previous studies have found that TRH can also stimulate mitochondrial activity in human epidermis and scalp HFs [26]. This invites the intriguing question whether the part of this TRH-induced increased mitochondrial activity, and thus energy metabolism is actually recruited to promote and support the energy intensive synthesis of selected keratins.

Thyroid-stimulating hormone is another key neurohormone involved in the regulation of keratin expression in human skin. TSH is expressed in the epidermis, and the gene encoding its receptor reportedly is also transcribed in the epidermis [14], while TSH-R protein is most prominently, if not exclusively, found in the skin mesenchyme, including the dermal sheath of human scalp HFs [18]. However, there is still a debate on the exact location of the TSH-R protein [13, 38]. In whole skin organ cultures, TSH stimulated the expression of K5 and K14, the two prototypic keratins that are expressed in the basal layer of the epidermis, connect to the hemidesmosomes in the basal side of the keratinocytes and are critical for keratinocyte function [6, 29]. Interestingly, TSH did not affect basal epidermal keratinocyte proliferation *ex vivo*, pointing to the fact that the upregulation of K5 and K14 was not just due to enhanced keratinocyte proliferation. Therefore, these findings suggest that TSH effects on

keratin expression are direct and independent of cellular proliferation changes. Just like with TRH, TSH was also found to enhance mitochondrial activity in the epidermis [27] and the HF epithelium [16], again raising the possibility of a coordinated, neurohormone-controlled increase in intraepithelial energy metabolism and keratin synthesis.

As alluded to above, keratin changes following TSH stimulation were also evident in human HFs *ex vivo*. Except for K5 in hair matrix keratinocytes, which was upregulated [18], all the other keratins examined were downregulated following TSH stimulation at the gene and protein levels. These included keratins expressed in the HF ORS, such as K6, K14, and K17, and hair keratins expressed in the hair cortex, such as K31, K32, and K85 [39]. While the exact mechanisms by which TSH changes keratin expression remains unknown, it is noteworthy that TSH also upregulated expression of MSX2 [39], a key transcription factor that controls keratin expression [40, 41]. It is also interesting to note that all these keratin changes were observed in the HF, although TSH itself does not affect hair growth, thus suggesting that these TSH-regulated changes in keratin expression do not translate into altered hair growth [18].

TRH has been found to enhance TSH expression in the human epidermis [13]. Since TSH can change keratin expression as we have just reviewed, it is possible that some of the effects of TRH on keratin expression are indirectly mediated by TSH. Indeed, some of the keratins that are modulated by TRH, such as K14, K17, and K85, are affected in a comparable manner by TSH [39].

3. The hypothalamus-pituitary-adrenal axis in the skin and its effects on keratin expression

Corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol form the HPA axis, which has a major role in controlling stress response by producing steroid hormones and regulatory peptides [9]. This axis is also active in human skin and HFs, where, namely, keratinocytes, but also other cutaneous cell populations act as both targets and also as nonclassical producers of these HPA constituents [10–12, 42, 43].

There are plenty of studies that report on the effect of glucocorticosteroids on keratin expression in the skin, effects that accompany physiological processes, such as wound healing [6]. Nevertheless, little is known on the effects of the other components of the HPA axis on keratin expression, and the available information is limited to CRH, which reportedly upregulates K1 and downregulates K14 in HaCaT cells and in human adult epidermal keratinocytes, as part of the induction of the terminal differentiation program [44, 45]. Taking into consideration the fact that the HPA is fully functional in human skin [2, 10–12], it is likely that additional keratins are regulated by these neuromediators, yet have escaped notice so far. Therefore, further research is warranted to explore this neuroendocrine frontier of keratin biology, namely, in human skin.

4. Prolactin effects on keratin expression

Prolactin and its receptor have been found to be expressed at the gene and protein levels in the human skin [19, 35, 46, 47], where they control a large number of functions, such as hair growth [19] and keratin expression (see below). Given the major role of prolactin in the

control of mammary development, growth, and milk production, it is not surprising that the first evidence for an effect of prolactin on keratin expression arose from mammary gland studies [48]. These studies have shown that if the prolactin receptor gene is knocked out, mice do not develop normal mammary buds, accompanied by decreased expression of selected keratins, such as K8, K17, K18, and K19 [48].

Since the mammary gland is basically a sweat gland-like derivative of the epidermis, and a prolactin-like protein has actually been found in human eccrine sweat glands [49], it was reasonable to hypothesize that prolactin may regulate keratin expression also in other skin appendages. Indeed, prolactin administration to organ-cultured human HFs resulted in upregulation of keratins expressed in the ORS, including K5 and K14, while the hair keratin K31 was downregulated *ex vivo* [50].

Perhaps the most interesting observation that emerged from this study was the stimulatory effect of prolactin on K15 and K19, that is, marker keratins for epithelial HF stem cells [51–53]. This stimulatory effect was reversed when a selective prolactin receptor antagonist was added to the culture medium. This effect was further confirmed when prolactin had a stimulatory effect on *KRT15* promoter activity *in situ* [50]. This finding strengthens the importance of prolactin as a stem cell promoting agent, as was also observed later in other classical prolactin target organs, such as the mammary gland [54]. Once again, this underscored the unique instructiveness of HFs as a discovery tool in skin research, namely, in cutaneous neuroendocrinology [2], from which novel, general neuroendocrine principles can be deduced.

Another important observation that emerged from these keratin studies was that the addition of a prolactin receptor antagonist alone also resulted in changes in keratin expression [50]. This shows that endogenous production of prolactin and/or prolactin receptor stimulation is an important element of normal skin physiology and homeostasis and is actually required to maintain the production of keratins in the HF. This is similar to the autocrine/paracrine effects attributed to prolactin also in the pituitary gland, where blocking of the prolactin receptor resulted in changes in cell turnover and prolactin receptor expression [55], and in extrapituitary locations such as the mammary gland, where changes in prolactin receptor patterning resulted in disruption of lobuloalveolar development [56].

It has been previously shown that there is an interplay between the different hormones and neurohormones in the skin and HFs, and that some of these connections are similar to those that exist in the pituitary. As an example, TRH can stimulate prolactin expression in the HF, while it can inhibit expression of the prolactin receptor [35]. Such an interplay is highly likely to also be at play in the regulation of keratin expression, and given that both neurohormones profoundly change the expression of selected keratins in human skin. Obviously, this adds another level of complexity to the challenge of segregating the direct effects of each of these neurohormones from indirect and cross-regulatory ones.

5. The effects of endocannabinoids on keratin expression

Accumulating data show that the endocannabinoid system (ECS) plays a major role in mammalian skin [57, 58]. Indeed, endocannabinoids are being produced by the epidermis and the skin appendages, including the HF, sweat glands, and sebaceous glands [58], and the

cannabinoid receptors CB_1 and CB_2 are prominently expressed on different skin cell populations [58]. Many different skin functions of the skin are now appreciated to be regulated by the ECS. For example, in the epidermis, it controls keratinocyte proliferation and differentiation, thereby affecting the epidermal barrier, and regulates melanogenesis [59–61].

The ECS also affects the skin appendages profoundly. Signaling via CB_1 inhibits hair growth and induces catagen, the regression phase of the HF [22, 62]. In sweat glands, anandamide stimulated sweat secretion of epithelial cells and reduced their proliferation [63]. The ECS can also affect sebaceous gland function, and by acting via CB_2, endocannabinoids positively control sebaceous lipid synthesis [64]. Furthermore, cannabidiol, a CB1 antagonizing nonpsychotropic phytocannabinoid, reduced sebocyte proliferation and normalized excess sebum production that can be observed in acne lesions [65, 66].

Taking into consideration its importance in epidermal keratinocyte function, it was not surprising that ECS modulation also affects keratin expression. For example, cannabinoid receptor activation on human HaCaT cells by the prototypic endocannabinoid, anandamide, inhibited cell differentiation, accompanied by reduced transcription of the *KRT1* and *KRT10* genes [67]. When tested in human skin culture and again in HaCaT cells, anandamide also inhibited K6 and K16 expression, independent of its antiproliferative properties [68]. Conversely, administration of the CB_1 antagonist, arachidonyl-2′-chloroethylamide (ACEA), upregulated K10 in human epidermis while decreasing the expression of K1 *ex vivo* [69].

Given its antiproliferative and differentiation-promoting effects in human epidermis as well as its overall largely anti-inflammatory properties (e.g., by reducing mast cell degranulation and maturation *in loco* [70]), CB ligands are coming under scrutiny as potential new therapeutics in the therapy of psoriasis [71]. If this line of research continues to be productive, it will become clinically even more important to dissect the relative contribution of CB-mediated changes in epidermal keratin expression to any beneficial effects observed by therapeutic CB stimulation. The use of ECS antagonists to change keratin expression underscores that, like we have seen in the case of prolactin, blocking the autocrine/paracrine effects of intracutaneously generated neuroendocrine mediators induces functionally relevant changes in human skin, such as altered keratin expression patterns.

6. Opioids and keratin expression

Murine and human skin both express opioid receptors, including the μ-, κ-, and δ-opioid receptors. Stimulation of these receptors participates in the control of melanocyte [72] and keratinocyte functions, such as impeding DNA synthesis and cell differentiation [73, 74]. Therefore, their connection to skin disorders, such as psoriasis, basal cell carcinoma, and wound healing, is currently under scrutiny [73, 75, 76].

As one might expect by now, opioid receptor ligands also induce changes in keratin expression. For example, the key endogenous ligand for the μ-opiate receptor, beta-endorphin, enhances the intraepidermal expression of K16 at the wound margin [77]. In psoriasis, a

hyperproliferative dermatosis, K16 expression is upregulated, and this is accompanied by downregulation of the μ-opiate receptor [75], and treatment of skin organ cultures with beta-endorphin resulted in elevated K16 production [75].

K10 is an additional keratin to be regulated by opioids, as mice knocked out for the δ-opioid receptor had enhanced K10 expression, together with a thinner epidermis [78], and the *Achillea millefolium* extract, a strong inducer of the μ-opioid receptor-1, led to increased differentiation of the cells in the epidermis with stronger K10 expression [79]. Yet, our current understanding of the role of opioid receptor-mediated signaling within the emerging neuroendocrine controls of keratin biology remains even more rudimentary than that of the neuromediators discussed further above.

7. Other neurohormones can alter keratin expression

Parathyroid hormone-related protein (PTHrP) is another important neuroendocrine mediator, which has importance in the normal formation of the mammary gland [80]. Keratin expression was tested in a K14 promoter-driven PTHrP mouse, and an overexpression of K17 in the nipple epidermis was evident in this mouse model [81]. Interestingly, PTHrP signaling affects BMP signaling and *Msx* gene activation, both of which are critical regulators of HF growth and function [80], just like PTHrP itself strongly modulates murine HF cycling [82, 83]. Yet, how PTHrP impacts on intrafollicular keratin remains to be evaluated.

Catecholamines can also change keratin expression, and when evaluated in limbal epithelial cells in culture, isoproterenol, a beta-adrenergic receptor agonist, led to pronounced changes in keratin expression [84]. When tested in HaCaT cells, the same compound stimulated differentiation, which was accompanied by increased K1 and K10 production [85].

In contrast, histamine led to decreased expression of differentiation markers in skin models and human keratinocyte cultures, among others, and also to decreased production of K1 and K10 [86]. The cholinergic system can also affect keratin expression. When tested in skin cultures *in vitro*, blocking of the cholinergic system resulted in decreased expression of differentiation markers, such as K2 and K10 [87]. Although these mediators clearly led to changes in keratin expression in these cases, it remains to be dissected whether these changes were due to a direct effect of the tested compound or reflected secondary events, resulting, for example, from changes in keratinocyte proliferation and differentiation.

8. Possible clinical implications of neuroendocrine-mediated changes in keratin expression

As reviewed in detail above, neuroendocrine mediators can change keratin expression in what appears to be a relatively selective manner. Let us now discuss, therefore, how this phenomenon might be translated into the treatment of several skin and hair conditions. This is

of special clinical relevance since neuromediator analogs, in principle, may be formulated to be topically applicable, thus circumventing or reducing the risk of undesired systemic effects. Some of the possible clinical scenarios for which such analogs may conceivably be used are described briefly below.

8.1. Treatment of keratin-related skin and hair genetic disorders

The list of genetic disorders linked to mutations in keratin genes continues to expand, and more than half of the keratin genes have been linked to a genetic disorder [88–92]. These disorders include ichthyoses, blistering disorders such as epidermolysis bullosa, hair conditions such as wooly hair and sparse hair, and changes in the normal growth of nails. A novel promising approach for the treatment of keratin disorders is the utilization of small molecule drugs to upregulate expression of compensatory keratins or to downregulate the expression of the mutated keratins [89, 93]. Such an approach has already been successful in several autosomal dominant keratin disorders, such as epidermolysis bullosa simplex and pachyonychia congenita [94–96].

It has also been reported to be of potential benefit in epidermolytic ichthyosis, an uncommon genodermatosis caused by mutations in keratins 1 or 10, when Reichelt et al. have shown that increased stability of keratins 5 and 14 could lead to the formation of normal epidermis in K10-null mice [97]. Furthermore, treatment of immortalized cell lines from a *KRT10*-mutated epidermolytic ichthyosis patient with all-trans retinoic acid led to a 200-fold decrease in mRNA expression of K10, accompanied by decreased keratin aggregation [98].

As reviewed above, the CB_1 agonist ACEA increased K10 expression, while reducing K1 production in human epidermis in culture [69]. Such changes could potentially be harnessed in epidermolytic ichthyosis patients to decrease the expression of mutated K1 while upregulating the expression of K10 that can functionally compensate in part for the mutated keratin. Given their differential regulation of distinct human keratins in human skin *ex vivo*, defined neuromediators now need to be systematically explored for their capacity to execute such therapeutically desirable reverse regulation of clinically relevant keratins in selected genodermatoses, perhaps starting with primary keratinocyte cultures derived from affected patients.

8.2. Treatment of inflammatory skin conditions (e.g., psoriasis)

Several inflammatory skin disorders are characterized by overexpression of K6. These include, for example, lichen planus and discoid lupus erythematosus [99]. However, the most prominent example is psoriasis, a chronic inflammatory skin condition, which is characterized by increased expression of K6, K16, and K17 [3, 68, 100]. K17 is probably of special importance in psoriasis pathogenesis, since it has been suggested to act as an antigenic target for T lymphocytes in the affected epidermis [101]. Furthermore, mice overexpressing K17 developed an inflammatory reaction and epidermal hyperplasia [102]. Moreover, K6, K16, and K17 expression pattern can impact on the cytokine or chemokine secretion of keratinocytes [102–105] and thus the intraepidermal inflammatory signaling milieu.

Therefore, compounds that can decrease the expression of these keratins might be therapeutically beneficial in these dermatoses, namely, in psoriasis, especially if they can also exert anti-inflammatory effects [106, 107], such as in the case of cannabinoid receptor agonists, which independently decrease the expression of K6 and K16 [68], combined with anti-inflammatory, antiproliferative, and antiangiogenic properties [3, 57, 71, 108, 109].

8.3. Wound healing

In healthy nonglabrous epidermis, K6, K16, and K17 are largely absent and not constitutively expressed by keratinocytes. However, in hyperproliferative states and conditions of epidermal stress, such as during wound healing, these keratins are rapidly upregulated and strongly expressed, since they play a major role in epidermal repair, as they are required for normal migration of keratinocytes from the wound edges and to ensure optimal closure of the wound [29, 110, 111]. Opiate receptor agonists that can boost wound healing are also stimulators for K16 expression, suggesting again the hypothesis of a coordinated neuroendocrine control of both, expression of optimally suited keratins and wound healing as such [77, 112]. Conceivably, therefore, neuroendocrine mediators that upregulate K6, K16, and K17 expression (e.g., catecholamines and endocannabinoids) might become therapeutically useful as promoters of re-epithelialization during wound healing.

8.4. Therapeutic regulation of stem cell-associated keratins

Prolactin increases the expression of the prototypic epithelial stem/progenitor cell-associated keratins, K15 and K19, [48, 50], and a continuous endogenous production of prolactin may be required to maintain normal K15 and K19 expression by these stem cells [50]. This raises the question whether neurohormones such as prolactin or related receptor agonists can be therapeutically recruited to ameliorate or prevent stem cell-based hair diseases characterized by permanent loss of the HF stem cell pool, such as lichen planopilaris or chemotherapy-induced alopecia [51, 113–115], or epidermal atrophy associated with an exhaustion of epidermal stem cell pools, as it occurs, for example, in connection with steroid therapy [116].

8.5. Hair growth

Keratins play a critical role in normal hair growth and structure. This is nicely exemplified by genetic hair disorders caused by keratin mutations [91]. When keratins that are produced in the hair cortex are mutated, the hair shaft is fragile and easy to break, and when the mutations are in keratins expressed in the most proximal part of the hair cortex, this leads to a more severe phenotype of complete hair loss [117, 118]. Instead, when keratins expressed in the IRS are mutated, this leads to a defect in hair curvature, oftentimes evident as wooly hair [90, 92, 119–121]. It is therefore conceivable that neuroendocrine manipulation of hair keratin expression may result in modulation of hair growth and/or hair shaft phenotype. It is therefore not surprising that TRH and prolactin, which both significantly modulate hair growth [2, 3, 23, 50, 122–126], also profoundly modulate hair keratin expression [37, 50].

One additional important aspect when discussing hair keratins is the presence and importance of KAPs. These proteins surround the keratin intermediate filaments in the hair shaft, cross-linking them by disulfide bonds [127], and providing them with rigidity and strength [128]. The number of KAPs is much higher than keratins, and 89 functional KAP genes have been described in humans [128], therefore there is probably a high degree of overlap between these proteins. Nevertheless, changes in KAPs could probably also affect hair structure. On this background, it is interesting to note that preliminary studies using microarrays in cultured HFs have revealed that certain neurohormones, such as TSH and prolactin, appear to alter the transcription of several KAP genes, such as KAP 4-4 and/or KAP 7-1 [18, 50]. These pilot observations deserve systematic follow up and may provide additional targets for therapeutic neuroendocrine intervention.

9. Conclusions

Here, we have reviewed that several neurohormones and neuropeptides generated in human skin as a nonclassical production site profoundly impact on the control of keratin expression. Specifically, we have presented TRH, TSH, opioids, prolactin, and cannabinoid receptor ligands as prominent examples for and indicators of a likely much more widespread and complex, evolutionarily conserved neuroendocrine regulation of human keratin biology *in situ* than we have come to appreciate so far. We have argued that this regulation is critically involved in the maintenance of skin and HF homeostasis and may participate in skin pathology. Thus, it is timely that mainstream keratin and neuroendocrinology research, which traditionally interconnect only rarely, discover the cross-fertilization potential and clinical relevance of systematically exploring the neuroendocrine control of keratin expression and its functional consequences, namely, in human skin and HFs. Besides defining some of the many open questions in the field, we have provided specific examples for how neurohormones may be harnessed to treat selected genodermatoses and other skin disorders accompanied by abnormal keratin expression.

Many obstacles encumber the ongoing journey toward understanding mechanistically how exactly these neuromediators change keratin expression on the molecular level, and in uncovering which of these effects are directly or indirectly mediated (e.g., by affecting other cutaneous functions, which then impact on keratin expression). This situation has been further complicated by increasing insight into the strong interplay between and cross-regulation of different neurohormones within human skin. However, recent advances and refinements of serum-free human skin and HF organ cultures, which permits the silencing of selected neurohormone and receptor genes [70, 129], and the use of selective neurohormone receptor antagonists [50] surely facilitate progress in this exciting, translationally relevant line of investigation.

Conflict of interest

The authors declare they have no conflicts of interest. For the record, however, RP is founder of Monasterium Laboratory, Münster/Germany (www.monasteriumlab.com), a hair and skin research company, and consults for several companies with an interest in skin and hair research.

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