Special Focus Review

Hormones and the pilosebaceous unit

Wen-Chieh Chen¹ and Christos C. Zouboulis^{2,3}

¹Department of Dermatology and Allergy; Technische Universität München; Munich, Germany; ²Departments of Dermatology, Venereology, Allergology and Immunology; Dessau Medical Center; Dessau, Germany; ³Laboratory of Biogerontology, Dermato-Pharmacology and Dermato-Endocrinology; Institute of Clinical Pharmacology and Toxicology; Charité Universitätsmedizin Berlin; Berlin, Germany

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Hormones can exert their actions through endocrine, paracrine, juxtacrine, autocrine and intracrine pathways. The skin, especially the pilosebaceous unit, can be regarded as an endocrine organ meanwhile a target of hormones, because it synthesizes miscellaneous hormones and expresses diverse hormone receptors. Over the past decade, steroid hormones, phospholipid hormones, retinoids and nuclear receptor ligands as well as the so-called stress hormones have been demonstrated to play pivotal roles in controlling the development of pilosebaceous units, lipogenesis of sebaceous glands and hair cycling. Among them, androgen is most extensively studied and of highest clinical significance. Androgen-mediated dermatoses such as acne, androgenetic alopecia and seborrhea are among the most common skin disorders, with most patients exhibiting normal circulating androgen levels. The “cutaneous hyperandrogenism” is caused by in situ overexpression of the androgenic enzymes and hyperresponsiveness of androgen receptors. Regulation of cutaneous steroidogenesis is analogous to that in gonads and adrenals. More work is needed to explain the regional difference within and between the androgen-mediated dermatoses. The pilosebaceous unit can act as an ideal model for studies in dermato-endocrinology.

Hormones are substances produced and released by cells to affect the other cells. The hormone action can be further divided into five categories according to the location of the target cells; (1) endocrine: the target cells are remote to the producing cells and will be reached via circulating blood, (2) paracrine: the target cells are in the neighborhood of the producing cells, (3) juxtacrine: the target cells are directly adjacent to the producing cells with connections in linkage,¹ (4) autocrine: the target cells are the producing cells per se, from which the hormones will be released and turn back, (5) intracrine: the target cells are also the producing cells but the synthesized hormones exert their action without release into the intercellular compartment.²

Hormones can be classified based on their chemical structures: (1) amino acid derivatives from tyrosine (e.g., thyroxine, epinephrine/norepinephrine, dopamine), from tryptophan (e.g., serotonin, melatonin), or from histidine (histamine); (2) oligopeptide hormones (e.g., oxytocin, vasopressin), polypeptide or protein hormones (e.g., α -melanocyte stimulating hormone, corticotropin releasing hormone, adrenocorticotrophic hormone) glycoprotein hormones (e.g., luteinizing hormone, human chorionic gonadotropin); (3) fatty acid derivatives such as steroid hormones (e.g., testosterone (T), estradiol) and phospholipids (prostaglandin E2 and prostaglandin F2 α). Hormones can be termed according to their origin; thyroid hormones are conventionally produced by thyroid glands, prostaglandins are first isolated from seminal fluid, and most neuromediators are initially identified in the nervous system. Hormones can be grouped together according to the target organs they work on, e.g., androgens and estrogens are sex hormones because they influence primarily the development and function of sexual organs. Hormones with identical molecular formation of the corresponding receptors are known to have close interaction in their functions, such as the steroid nuclear receptor superfamily encompassing steroid hormone receptors, thyroid hormone receptors, retinoid receptor, vitamin D receptor and peroxisome proliferator-activated receptors. However, these conventional concepts of hormone classifications have been complicated by the identification of diverse sources of hormones, multiplicity of hormone actions and extensive distribution of hormone receptors. For example, human skin has been demonstrated to be able to produce many steroid hormones and neuromediators, and meanwhile to express the corresponding receptors.³⁻⁵ There is substantial experimental evidence indicating the influence of sex hormones on immunity and allergy development,⁶ and the effect of neuromediators on the physiology and pathology of pilosebaceous units.^{4,5} The hormone research in dermatology, coined as “Dermato-Endocrinology”, is characterized by the following hallmarks: (1) skin is an endocrine organ per se and can synthesize diverse hormones; (2) skin is also the target of hormones and expresses many more hormone receptors as have been identified; (3) the hormones generated in or by the skin can exert systemic effects; (4) the “intracrine action” is very important for hormone effects on the skin, especially regarding sex hormones.⁷

Within the skin, the pilosebaceous unit is the main factory for hormone production.³ Moreover, the complexity of hair cycle and the active lipogenesis of sebaceous glands have stimulated the study on the expression of miscellaneous hormone receptors in the

*Correspondence to: Wen-Chieh Chen; Department of Dermatology and Allergy, Technische Universität München, Biedersteinerstrasse 29, 80802 Munich; Germany; Email: wenchieh65.chen@gmail.com/ Christos C. Zouboulis; Departments of Dermatology, Venereology, Allergology and Immunology; Dessau Medical Center; Auenweg 38; Dessau 06847 Germany; Tel.: +49.340.5014000; Fax: +49.340.5014025; Email: christos.zouboulis@klinikum-dessau.de

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pilosebaceous unit. Table 1 summarizes the current understanding of the expression of various hormones and their receptors in the pilosebaceous unit based on the chemical structure of hormones.⁸⁻⁷³ There is overlapping as well as discrepancy between sebaceous glands and hair follicles. Most well studied are steroid hormones, their releasing hormones and retinoids. Rapidly increasing knowledge has been obtained from the studies on neuromediators and phospholipids (eicosanoids). Of high potential is the research on the role of adipose tissue hormones or adipokines in sebocyte biology.⁷⁴ Not much is known about the expression of exocrine hormones in the pilosebaceous unit.

Androgens are among the most well studied hormones in cutaneous biology. The classical androgen-dependent dermatoses, acne, androgenetic alopecia (AGA), seborrhea and hirsutism are among the most common skin disorders. Human sebaceous glands and hair follicles are equipped with all the necessary enzymes for biosynthesis and metabolism of androgens. Androgens can be generated via de novo synthetic pathway from cholesterol to T and dihydrotestosterone (DHT), or/and via a shortcut pathway from the circulating dehydroepiandrosterone sulfate (DHEAS).⁷⁵ Four "upstream" enzymes including steroidogenic acute regulatory protein (StAR), cytochrome P450 cholesterol side-chain cleavage enzyme (P450_{scc}) and cytochrome P450 17 α -hydroxylase/17,20-lyase (P450_{c17}) and steroid 3 β -hydroxysteroid dehydrogenase (3 β -HSD) are responsible for the early steps of androgenesis from cholesterol to DHEA, while four additional "downstream" enzymes including steroid sulfatase and 5 α -reductase work for the formation of DHT from DHEAS to amplify the androgenic effects, or 3 α -HSD and aromatase function to reduce androgen levels.

DHT is converted from T under the action of 5 α -reductase and both bind to the same androgen receptor (AR).⁷⁶ The cutaneous expression of AR was demonstrated mainly in epidermal keratinocytes, sebaceous glands and hair dermal papilla cells (DPC), with restricted expression in dermal fibroblasts, sweat gland cells, endothelial cells and genital melanocytes.^{49,50} In sebaceous glands, AR was detected only in the basal, early differentiated sebocytes. Conflicting data exist in the exact pattern of AR expression in human hair follicles, especially concerning their expression in occipital scalp.^{77,78} The AR expression was found mainly in the DPC but absent in the keratinocytes of outer root sheath (including the bulge regions supposed to contain the hair stem cells) and of the inner root sheaths.⁷⁹ On the other hand, higher levels of AR were detected in the DPC from balding hair follicle as compared to non-balding scalp.⁸⁰

Studies of the androgenic effect on acne formation have been mainly focused on the sebum production, which is the process of sebocyte differentiation and lipogenesis. In primary cultures of human sebocytes, both T and DHT showed a stimulatory effect on sebocyte proliferation, although the in vitro effect was usually observed at above the physiological concentration in most studies.^{81,82} In sebaceous gland organ culture, T and DHT at physiological concentrations demonstrated no or inhibitory effect on rates of cell division or lipogenesis.⁸³ However, combination of T and linoleic acid exhibited a synergistic effect on lipid synthesis in SZ95 sebocytes.⁸⁴ On the other hand, it remains to be determined if higher activity of the type I 5 α -reductase detected in the follicular infundibulum is associated with the abnormal hyperproliferation/dyskeratinization of keratinocytes in this region, leading to formation of microcomedones.⁸⁵ It is worthwhile to

Table 1 Biosynthesis of hormones and expression of hormone receptors in the human pilosebaceous unit based on the chemical structure of hormones

Hormones/hormone receptors	Sebaceous glands	Hair follicles	References
Amino acids			
Tyrosine			
thyroxine/thyroxine receptor	±/+	±/+	8, 9
epinephrine/adrenergic receptor	±/-	±/±	10, 11
norepinephrine/adrenergic receptor	±/-	±/±	10, 11
dopamine/dopamine receptor	±/±	±/±	12
Tryptophan			
serotonin	+/?	+/?	13
melatonin/melatonin receptors	±/±	+/+	14
Histidine			
histamine/histamine receptor-1	±/+	±/±	15
Oligopeptides (2–10 amino acids)			
oxytocin/oxytocin receptor	±/+*	±/±	
antidiuretic hormone/vasopressin receptor	±/±	±/±	
thyrotropin releasing hormone (THR)/TRHR	±/±	±/±	
gonadotropin releasing hormone (GnRH)/GnRHR	±/±	±/±	
prolactin releasing hormone (PRH)/PRLHR	±/±	±/±	
substance P/neurokinin-1 receptor	±/+	±/+	16
neurokinin A/neurokinin-2 receptor	±/±	±/±	
neurokinin B/neurokinin-3 receptor	±/±	±/±	
angiotensin/angiotensin receptor	±/±	±/+	17
Polypeptides/proteins (> 10 amino acids)			
corticotropin releasing hormone (CRH)/CRH-R2	+/+	+/+	18, 19
growth hormone releasing hormone (GHRH)/GHRH receptor	±/±	±/±	
growth hormone (GH)/GHR	±/+	±/+	20
adrenocorticotrophic hormone (ACTH)/MC1R	+/+	+/+	21
prolactin/prolactin receptor	±/+	+/+	22
α -melanocyte stimulating hormone (α -MSH)/MCR-1, MCR-5	+/+	+/+	23–27
atrial natriuretic hormone (ANF)/ANF receptor	±/±	±/±	
insulin/insulin receptor	±/±	±/±	
glucagon/glucagon receptor	±/±	±/±	
Insulin-like growth factor-I (IGF-I)/IGF-I receptor	±/+	±/+	28, 29
somatostatin/somatostatin receptor 1–5	±/+	±/+	30
gastrin/gastrin receptor	±/±	±/±	
endothelin/endothelin receptor	±/±	+/+	31, 32
secretin/secretin receptor	±/±	±/±	
cholecystokinin/cholecystokinin receptor	±/±	±/±	

Table 1, cont. **Biosynthesis of hormones and expression of hormone receptors in the human pilosebaceous unit based on the chemical structure of hormones**

parathyroid hormone (PTH)/PTHr	±/±	±/±	
parathyroid hormone related protein (PTHrP)/PTHrP receptor	±/±	+/?	33
calcitonin/calcitonin receptor	±/±	±/±	
adrenomedullin/calcitonin receptor-like receptor	+/?	+/?	34
erythropoietin/erythropoietin receptor	±/±	+/?	35
(pro)rennin/(pro)renin receptor	±/±	±/±	
ghrelin/ghrelin receptor	±/±	±/±	
leptin/leptin receptor	-/?	+/?	36
adiponectin/adiponectin receptor	±/±	±/±	
resistin/resistin receptor	+/?	+/?	37
orexin/orexin receptor	±/±	±/±	
activin/activin receptor	±/±	±/±	
inhibin/inhibin receptor	±/±	±/±	
neuropeptide Y/neuropeptide Y receptor	±/±	±/±	
epidermal growth factor (EGF)/EGFR	±/+	±/+	38, 39
fibroblast growth factor (FGF)/FGFR		+/?	40, 41
vascular growth factor (VGF)/VGFR	±/±	+/?	42, 43
hepatocyte growth factor (HGF)/HGFR	±/±	+/?	41, 44
transforming growth factor-β (TGFβ)/TGFβ receptor	±/±	+/?	41, 45
Glycoproteins			
follicular-stimulating hormone (FSH)/FSH receptor	±/±	±/±	
luteinizing hormone (LH)/LH receptors	+/?	+/?	46, 47
thyroid stimulating hormone (TSH)/TSHR	±/±	±/±	
chorionic gonadotropin (hCG)/hCG receptor	+/?	+/?	46, 47
follicle-stimulating hormone receptor	±/±	±/±	
platelet-derived growth factor (PDGF)/PDGFR	+/?	+/?	41, 48
Lipids/steroids			
androgens/androgen receptor	+/?	+/?	49, 50
estrogens/estrogen receptor	±/+	+/?	49, 51, 52
progesterone/progesterone receptor	+/?	+/?	49, 53
glucocorticoid/glucocorticoid receptor	±/+	+/?	22, 54
aldosterone/aldosterone receptor	±/+	±/+	55
1,25 dihydroxy-vitamin D3/VDR	+/?	±/+	56–58
endocannabinoids/cannabinoid receptors	+/? (CB-2)	+/? (CB-1)	59, 60
Phospholipids			
prostaglandin E2/EP	+/?	+/?	61, 62
prostaglandin F2α/FP	±/-*	+/?	62, 63

Table 1, cont. **Biosynthesis of hormones and expression of hormone receptors in the human pilosebaceous unit based on the chemical structure of hormones**

prostaglandin D2/DP	±/±	±/+	63
prostaglandin I2/IP	±/±	±/+	63
thromboxane A2/TP	±/±	±/+	63
prostaglandin J2/PPAR-γ	±/+	±/+	64, 65
leukotriene B4/BLT	+/?	±/±	61
Retinoids and other endogenous nuclear receptor ligands			
retinoids/retinoid receptors	+/?	+/?	66–68
free fatty acids, leukotriene B4/PPAR-α	+/?	±/+	61, 64, 65
free fatty acids/PPAR-β, -δ	+/?	+/?	64, 65, 69, 70
22(R)-hydroxycholesterol/liver X receptors	±/+	±/+	71, 72
bile acids/farnesoid X receptor	±/-	±/±	73
endobiotics/pregnane X receptor	±/+	±/±	73

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examine if androgens can also influence the inflammation and scarring formation during the acne development.

AGA can be defined as a DHT-dependent process with continuous miniaturization of androgen sensitive hair follicles in the fronto-parietal scalp. However, as most men with AGA, similar to men with acne, have normal circulating levels of androgens, the "cutaneous hyperandrogenism" is hypothesized to be caused by (1) overproduction of androgens in the pilosebaceous units due to enhanced expression and activity of androgenic enzymes, or/and (2) overexpression or hyperresponsiveness of androgen receptors. The former has been supported by the increased expression and enzyme activity of StAR, 3β-HSD, 17β-HSD and 5α-reductase leading to high follicular levels of DHT.^{75,86,87} Moreover, studies of the cutaneous expression of sex-determining genes in regulating steroidogenesis showed significantly higher protein levels of DAX-1, SRY and WT-1 in the bald fronto-parietal scalp as compared to the occipital scalp, in which only the SRY expression displayed a positive correlation with the baldness severity in Norwood-Hamilton classification.⁸⁸ On the other hand, higher levels of AR were found in the balding hair follicle DPC than those from non-balding scalp,⁸⁰ and AR polymorphism was suggested to confer susceptibility to AGA.⁸⁹ Highly interesting are regional differences in cutaneous hyperandrogenism, in which (1) people with acne may not have AGA and vice versa; (2) AGA involves almost exclusively the frontoparietal scalp sparing the occipital scalp; (3) acne lesions tends to move from forehead/cheeks in pubertal acne to lower face/submandibular regions in acne tarda. There are some explanations for the contradictory androgen actions on hair follicles from different anatomic sites or between men with and without AGA: (1) absence of AR in DPC from occipital scalp;⁹⁰ (2) the expression of AR co-activator

was higher in DPC from beard and bald frontal scalp but lower in cells from occipital scalp;⁹¹ (3) androgen significantly stimulated the proliferation of keratinocytes co-cultured with beard DPC via insulin-like growth factor-I, while the inhibitory effect of androgen on the growth of keratinocytes co-cultured with DPC from AGA was mediated by TGF β 1 in a paracrine manner;⁹² (4) differences in the expression of specific biomarkers in beard vs. scalp DPC;⁹³ (5) higher concentrations of DHT and T could cause apoptosis in human DPC from nonbalding occipital scalp;⁹⁴ (6) significant suppression of Wnt signal-mediated transcription in response to DHT treatment was observed only in DP cells from AGA patients.⁹⁵

The situation in women is much more complicated; hyperandrogenemia can be found in about 50% the women with only mild hirsutism and in 33% with only minor acne.⁸⁷ However, no correlation exists between acne severity and any other clinical or laboratory markers of androgenicity in women, which suggests that in most cases factors other than hyperandrogenemia are necessary for the development of acne.⁹⁷⁻⁹⁹ It has been widely accepted that female AGA represents the female counterpart to male AGA, and they share similar changes in histology (hair follicle miniaturization) and biochemistry (increased DHT levels in the affected scalp). However, there are some evidence indicating that they are different entities and challenging the role of androgens;¹⁰⁰ (1) a young woman with hypopituitarism presented with typical clinical and histological features of female AGA in the absence of detectable levels of circulating androgens;¹⁰¹ (2) modest efficacy of anti-androgen therapy for female AGA in comparison to the male counterpart; (3) AGA can occur in children before puberty.¹⁰² A recent genome wide study even casted doubt on the omnipotent role of androgen in male AGA.¹⁰³

In conclusion, the human pilosebaceous unit can synthesize varieties of amino acid, oligopeptide, polypeptide/protein, glycoprotein, lipid/phospholipid hormones and retinoids, which can function in a paracrine, autocrine and intracrine pathway. There exist more diverse hormone receptors in the pilosebaceous unit to take up and interact with the circulating message released from other endocrine organs. Therefore, the human pilosebaceous unit can work as an ideal model for dermato-endocrinological studies. In correlation with clinical observations, further molecular studies are needed to understand the function and interaction of the various identified hormones/hormone receptors in the pathogenesis of skin diseases.

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