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Review

The human skin as a hormone target and an endocrine gland

Christos C. Zouboulis

Department of Dermatology, Charité University Medicine Berlin, Campus Benjamin Franklin, Berlin, Germany

ABSTRACT

Hormones influence the development and function of human skin which also produces and releases hormones. Recently attention has been focused on identifying and understanding the complex endocrine properties of human skin, such as expression and function of specific hormone receptors, synthesis of hormones from major classes of compounds used by the body for general purposes, organized metabolism, activation, inactivation and elimination of the hormones in specialized cells of the tissue, exertion of biological activity and release of tissue hormones in the circulation. Specifically, hormones exert their biological effects on the skin through interaction with high-affinity receptors, such as several receptors for peptide hormones and neurotransmitters, steroid and thyroid hormones. Hormones exhibit a wide range of biological activities on the skin with distinct effects caused by growth hormone/insulin-like growth factor-I, neuropeptides, sex steroids, glucocorticoids, retinoids, vitamin D, peroxisome proliferator-activated receptor ligands, eicosanoids, melatonin and serotonin. Human skin produces, activates or inactivates metabolically numerous hormones which are probably important for skin functions but also for functions of the entire human organism, such as sex hormones, especially in aged individuals, insulin-like growth factor and -binding proteins, neuropeptides, prolactin, catecholamines, retinoids, steroids, vitamin D and eicosanoids. These functions are undertaken in most cases by different skin cell populations in a coordinated way, indicating the endocrine autonomy of the skin. Characteristic examples are the metabolic pathways of the corticotropin-releasing hormone/propiomelanocortin axis, steroidogenesis, vitamin D and retinoids. The human skin is, thus, the largest, peripheral endocrine organ.

Key Words: Human skin, Endocrinology, Hormone synthesis, Hormone receptors, Hormone metabolism, Hormone activity

INTRODUCTION

The human skin is classically regarded as the target for several hormones whose effects have long been recognized and in some instances well characterized[1]. For example, hair follicles and sebaceous glands are the targets for androgen steroids secreted by the gonads and the adrenal cortex[2,3] and melanocytes are directly influenced by polypeptide hormones of the pituitary[4]. In addition, hormones play an important role in the development and the physiological function of human skin tissues[5,6]. From the modern dermato-endocrinologic point of view, the skin is not only the recipient of signals from distant transmitters but is also an organized community in which the cells and

Address correspondence and requests for reprints to:
Prof. Dr. Christos C. Zouboulis, Department of Dermatology, Charité University Medicine Berlin, Campus Benjamin Franklin, Fabeckstrasse 60-62, 14195 Berlin, Germany,
Tel.: +49-30-84456910, Fax: +49-30-84456908,
e-mail: zouboulis@medizin.fu-berlin.de

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organelles emit, receive and coordinate molecular signals from a seemingly unlimited number of distant sources, their neighbors and themselves[7]. In the widest sense, the human skin and its cells are the targets as well as the producers of hormones. For example, the circulating androgens dehydroepiandrosterone (DHEA) and androstenedione are converted in the skin to testosterone and further to 5a-dihydrotestosterone (5a-DHT)[3,8].

Despite this widely accepted knowledge, focus on the complex endocrine properties of the human skin has been directed only recently[1,5,7]. New data have rapidly accumulated in the last three years regarding expression and function of specific hormone receptors, synthesis of hormones from major classes of compounds used by the body for general purposes, organized metabolism, activation, inactivation and elimination of the hormones in specialized cells of the tissue, exertion of biological activity and release of hormones in the circulation, and these are included in this review.

THE HUMAN SKIN AS HORMONE TARGET

Hormone Receptors

Hormones exert their biological effects on the skin through binding and interaction with high-affinity receptors. The human skin expresses receptors for peptide hormones and neurotransmitters, which are mostly aligned on the cell surface, and for steroid and thyroid hormones, which are found in the cytoplasm or nuclear compartments (Figure 1).

Receptors for peptide hormones and neurotransmitters: Three of four groups of peptide hormone and neurotransmitter receptors are represented in human skin. The so-called serpentine or "seven transmem-

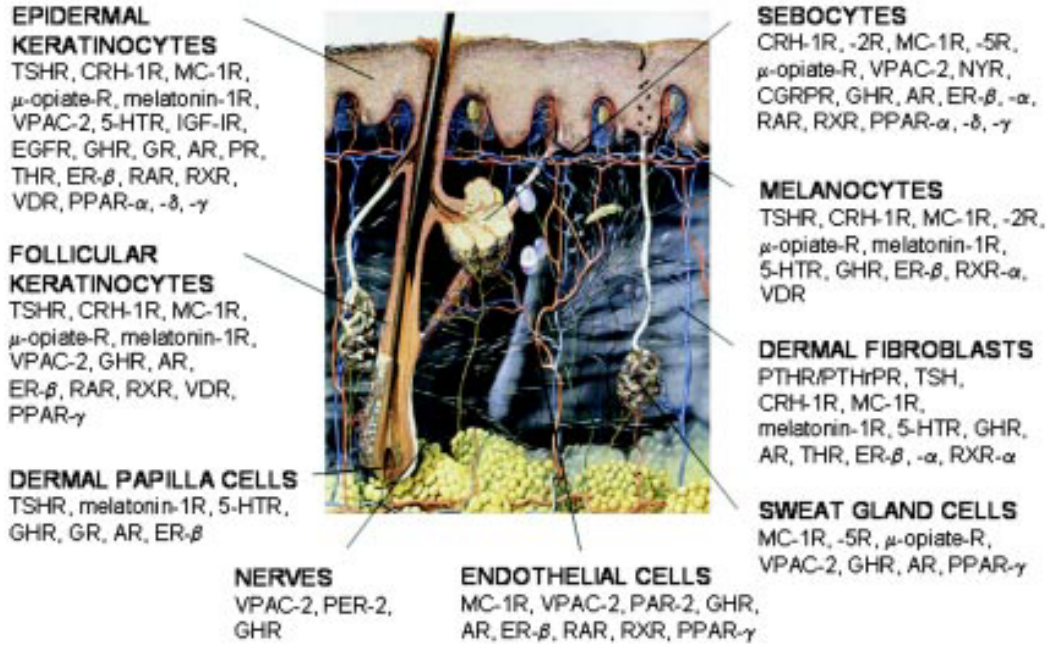

Figure 1. Hormone receptors detected as being active in human skin cells. PTHR/PTHrPR, parathyroid hormone receptor/parathyroid hormone-related peptide receptor; TSHR, thyroid-stimulating hormone receptor; CRH-1R, -2R, corticotropin-releasing hormone receptors types 1 and 2; MC-1R, -2R, -5R, melanocortin receptor types 1, 2 and 5; μ-opiate-R, μ-opiate receptors; melatonin-1R, melatonin receptor type 1; VPAC-2, vasoactive intestinal popypeptide receptor type 2; NYR, neuropeptide Y receptor; CGRPR, calcitonin gene-related peptide receptor; 5-HTR, serotonin receptors (5-hydroxytryptamine receptors); PAR, proteinase-activated receptors; IGF-IR, insulin/insulin-like growth factor I receptor; GHR, growth hormone receptor; GR, glucocorticoid receptor; AR, androgen receptor; PR, progesterone receptor; THR, thyroid hormone receptors (isotypes a1 and b1); ER-β, -α, estrogen receptor types β and α; RAR, retinoic acid receptors; RXR, retinoid X receptors; RXR-α, retinoid X receptor type α; VDR, vitamin D (calcitriol) receptor; PPAR-α, -δ, -γ, peroxisome proliferator-related receptors types α, δ, γ.

brane domain" receptors contain an amino terminal extracellular domain followed by seven hydrophobic aminoacid segments, each of which spans the membrane bilayer. The seventh segment is followed by a hydrophilic carboxyl terminal domain, which resides within the cytoplasmic compartment. To this group belong:

a) the *parathyroid hormone (PTH)/parathyroid hormone-related peptide (PTHrP) receptor* which is expressed in dermal fibroblasts but not in epidermal keratinocytes[9,10];

b) the *thyroid-stimulating hormone (TSH) receptor* which is present in epidermal, follicular and neonatal keratinocytes, epidermal melanocytes and dermal and dermal papilla fibroblasts[11];

c) the *corticotropin-releasing hormone (CRH) receptors* from which type 1 is predominant in human skin, being present in epidermal and follicular keratinocytes, melanocytes and dermal fibroblasts, whereas sebocytes express types 1 and 2[12,13];

d) the *melanocortin receptors (MC)*, among them MC1 which presents high affinity for a-melanocyte-stimulating hormone (α-MSH) and adrenocorticotropic hormone (ACTH) and is expressed in epidermal and follicular keratinocytes, epidermal and follicular melanocytes, sebocytes, sweat gland cells, endothelial cells, Langerhans cells, monocytes, macrophages, lymphocytes and dermal fibroblasts, MC2 which is specific for ACTH and is expressed in epidermal melanocytes and adipocytes, and MC5 which shows affinity for α-MSH and ACTH and is present in sebocytes, sweat gland cells and adipocytes[12,14-17]. MC5 but not MC1 expression can be enhanced after treatment of cultured sebocytes with α-MSH[17];

e) the *μ-opiate receptors* which bind with high affinity β-endorphin and are expressed in epidermal and outer root sheath keratinocytes, melanocytes, sebocytes and cells of the sweat gland secretory portion[12,18,19];

f) the *melatonin receptors* type 1, which is the predominant variant expressed in normal adult epidermal, follicular and neonatal keratinocytes, epidermal melanocytes, and in dermal and hair follicle papilla fibroblasts, and type 2 which has been detected only in neonatal keratinocytes[20];

g) the *vasoactive intestinal popypeptide (VIP) receptors (VPAC)* which are expressed in epidermal keratinocytes, with VPAC2 exhibiting the most pronounced expression in keratinocytes of the basal layer and in glandular cells surrounded by VIP-immunoreactive nerve fibers, hair follicle cells next to VIP-positive fibers, sebocytes, sweat gland cells, endothelial cells, mononuclear cells and dermal nerve fibers[21-24];

h) the *neuropeptide Y receptor* which is present in sebocytes[23];

i) the *calcitonin gene-related peptide (CGRP) receptor* which is expressed in sebocytes and Langerhans cells[23,25];

j) *the serotonin receptors (5-hydroxytryptamine receptors, 5-HTR)* which can be categorized into seven families (5HTR1-7) and include at least 21 subtypes[26]. They are cation-selective transmitter-gated ion channels of the Cys-loop superfamily. 5HTR1A, 5HTR1B and 5HTR2A expression was detected in epidermal keratinocytes, melanocytes and dermal fibroblasts, whereas 5HTR2A is also expressed in dermal papilla fibroblasts. 5HTR2C mRNA message was found in follicular melanocytes, dermal papilla fibroblasts and dermal fibroblasts. The 5HTR2B and 5HTR7 variants were generally detected in normal skin[20]; and

k) the *proteinase-activated receptors (PARs)* represent a unique subclass of G-protein-coupled receptors of which four family members have now been cloned from a number of species[27]. The novel mechanism of receptor activation involves the proteolytic unmasking of a cryptic N-terminal receptor sequence that, remaining tethered, binds to and triggers receptor function. In addition, short (5-6 aminoacids) synthetic peptides, based on the proteolytically revealed motif can activate PARs without the unmasking of the tethered ligand. In the skin, PAR-2 is expressed on sensory neurons and endothelial cells and may have high impact in regulating cutaneous neurogenic inflammation[28].

The second group includes insulin/insulin-like growth factor I (IGF-I) receptor and the epidermal growth factor (EGF) receptor which are expressed in epidermal keratinocytes[29,30] and belong to the single-transmembrane domain receptors that harbor intrinsic tyrosine kinase activity.

The third group, which is functionally similar to the second group, is characterized by a large extracellular binding domain followed by a single membrane spanning segment and a cytoplasmic tail. These receptors do not possess intrinsic tyrosine kinase activity but appear to function through interaction with soluble transducer molecules which do possess such activity. In human skin, they are represented by the growth hormone (GH) receptor which is present in melanocytes and dermal fibroblasts, epidermal and follicular keratinocytes of the outer root sheath, especially the basal ones, sebocytes, cells of the sweat gland secretory duct, hair matrix cells of the dermal papillae, endothelial cells, Schwann cells of peripheral nerve fascicles and adipocytes of the dermis[29,31,32].

Steroid hormone and thyroid hormone receptors: The nuclear receptors differ from the receptors of the cell membrane in that they are soluble molecules with a proclivity for employing transcriptional regulation as a means of promoting their biological effects. Thus, though some receptors are compartmentalized in the cytoplasm and others are confined to the nucleus, they all operate within the nucleus chromatin to initiate the signaling cascade. They associate in the nucleus with DNA sequences bearing a specific recognition element called "hormone response element". Hormone response elements have different canonical sequences for each hormone. These receptors are expressed in human skin and can be grouped into two major subtypes groups based on shared structural and functional properties.

The first group, the steroid receptor family, includes:

a) the *glucocorticoid receptor* which is mainly expressed in basal keratinocytes, Langerhans cells and dermal fibroblasts[33,34];

b) the *androgen receptor (AR)* which is present in epidermal and follicular keratinocytes, sebocytes, sweat gland cells, dermal papilla cells, dermal fibroblasts, endothelial cells and genital melanocytes[3,35-37]; and

c) the *progesterone receptor* which is expressed in basal epidermal keratinocytes only[38].

While the glucocorticoid receptor is down-regulated by its ligands in dermal fibroblasts[39], AR is stabilized by ligand binding und up-regulated in fibroblasts and sebocytes[40,41]. Steroid receptors under basal conditions exist as cytoplasmic, polymeric complexes that include the heat shock proteins hsp 90, hsp 70 and hsp 56. Association of the steroid ligand with the receptor results in dissociation of the heat shock proteins. This in turn exposes a nuclear translocation signal previously buried in the receptor structure and initiates transport of the receptor to the nucleus.

The second group, the thyroid receptor family, includes

a) the *thyroid hormone receptors* (isotypes a1 and b1) which are present in epidermal keratinocytes and dermal fibroblasts[42,43];

b) the *estrogen receptors* with the β-isotype being strongly expressed in the skin detected in epidermal and outer root sheath keratinocytes, melanocytes, dermal fibroblasts, dermal papilla cells, sebocytes, endothelial cells and adipocytes[37,44-47,] and the α-isotype found in sebocytes and dermal fibroblasts in vitro[44,47].

c) the *retinoic acid receptors (RAR*; isotypes α and γ) and *retinoid X receptors (RXR*; isotypes α, β, γ) which are expressed in epidermal keratinocytes of the stratum granulosum, follicular keratinocytes, sebocytes and endothelial cells, while only the RXRa isotype is present in melanocytes, fibroblasts and inflammatory cells[48-52];

d) the *vitamin D receptor (VDR)* which is present in keratinocytes of all epidermal layers except those of the stratum corneum, epithelial cells of the epidermal appendages, melanocytes, Langerhans cells, CD11b+ macrophages and CD3+ T-lymphocytes[53,54]; and

e) the *peroxisome proliferator-related receptors (PPAR)* which are expressed in epidermal and follicular keratinocytes, sebocytes, sweat gland cells, endothelial cells and adipocytes (isotype γ), whereas isotypes α and δ are also expressed in keratinocytes and sebocytes[55,56]. PPARδ is the predominant PPAR subtype in human keratinocytes and is highly expressed in basal cells and suprabasal cells.

The members of the thyroid receptor family share a high degree of homology to the proto-oncogene *c-erb*A and high affinity for a common DNA recognition site. With the exception of the estrogen receptor, they do not associate with the heat shock proteins and

are constitutively bound to chromatin in the nucleus. The estrogen receptor, though demonstrating an association with heat shock proteins, is largely confined to the nuclear compartment[47]. The estrogen receptor binds to its regulatory element as a homodimer, while the other receptors of this family prefer to bind as heterodimers together with a RXR molecule. The latter amplifies both the DNA binding and the functional activity of the receptor.

Biological Activity of Hormones in Human Skin

PTHrP: The PTHrP inhibits proliferation of dermal fibroblasts in a dose dependent manner, whereas a dose-dependent stimulation of cAMP, released by fibroblasts, can be concomitantly observed[57]. In contrast, PTHrP has no effect on collagen synthesis, whereas it increases metalloproteinase 2 activity. Modulation of the PTH / PTHrP receptor on dermal fibroblasts increases the membrane-associated protein kinase C activity modulating proliferation of epidermal keratinocytes in a paracrine manner[58].

CRH: CRH has recently been shown to stimulate sebaceous lipogenesis[13]. On the other hand, CRH inhibits proliferation of keratinocytes and enhances immunoactivity by up-regulating the interferon-gamma-stimulated expression of the hCAM and ICAM-1 adhesion molecules and of the HLA-DR antigen[59]. All these effects are concentration-dependent with maximal activity at CRH 10^{-7} M.

POMC peptides: There is increasing evidence that the cutaneous nervous system modulates physiological and pathophysiological effects including cell growth and differentiation, immunity and inflammation as well as tissue repair. Both cutaneous nervous fibers and inflammatory cells are able to release neuromediators and thereby activate specific receptors on target cells in the skin. POMC peptides are likely to play a major role in the regulation of the skin pigmentary system[4,60] and of cutaneous inflammation[14,28]. ACTH and α-MSH bind to MC1 of melanocytes and exhibit the most significant melanogenic activity via cAMP-dependent pathways and tyrosinase activation, which is enhanced by ultraviolet light[12]. Melanogenesis is a highly regulated process modified by postranslational, translational or transcriptional mechanisms. In addition, dendrite formation and stimulation of melanocyte proliferation by POMC peptides have been reported. α-MSH can also stimulate attachment of melanocytes to laminin and fibronectin and inhibit TNF-α-stimulated expression of ICAM-1.

In keratinocytes, α-MSH stimulates cell proliferation, down-regulates expression of hsp 70[61] and modulates cytokine production with up-regulation of IL-10 and inhibition of the IL-1-induced production and secretion of IL-8[14,28]. The latter effect was also detected in fibroblasts, where it may be mediated by NF-kB and AP-1[62]. α-MSH also stimulates synthesis and activity of collagenase/matrix metalloproteinase-1 in dermal fibroblasts[63]. TNF-α addition resulted in increased β-endorphin and ACTH levels[12]. In contrast, tumor growth factor-β (TGF-β)-stimulated fibroblasts showed no alteration in β-endorphin and α-MSH levels, whereas ACTH release was significantly enhanced.

On the other hand, it is likely that overproduction of ACTH may prolong the anagen phase of the hair cycle[12]. In sebocytes, α-MSH was shown to stimulate proliferation through its binding to MC1 and lipid synthesis through binding to MC5[15,17]. α-MSH may play a crucial role in endothelial cell function by decreasing the adherence and transmigration of inflammatory cells, a prerequisite for immune and inflammatory reactions[12]. The POMC peptides have strong immunomodulatory potential resulting in an overall immunosuppressive effect with α-MSH presenting the widest spectrum of activities[14], such as suppression of the contact hypersensitivity reaction to nickel by systemic or topical application[12]. α-MSH in vitro was found to down-regulate costimulatory molecule expression on dendritic cells and in vivo via the generation of suppressor T-lymphocytes to induce hapten specific tolerance[28]. Both α-MSH and β-endorphin induced histamine release from human foreskin mast cells in vitro[64].

γ-MSH also seems to exercise some control over the cutaneous inflammatory process by similar mechanisms to those of α-MSH, namely down-regulating the production of proinflammatory cytokines, while the production of the anti-inflammatory cytokine IL-10 is stimulated[65].

In addition to its effect on mast cells, β-endorphin was shown to stimulate cytokeratin 16 expression and down-regulate μ-opiate receptor expression in human epidermis[66]. On the other hand, β-endorphin has po-

tent melanogenic, mitogenic and dendritogenic effects in cultured epidermal melanocytes[18]. In sebocytes, β-endorphin inhibits the EGF-induced proliferation and stimulate lipogenesis[19].

Melatonin: Melatonin inhibits both apoptosis of keratinocytes incubated in serum-free media and proliferation of keratinocytes cultured in medium supplemented with serum. It increases the numbers of viable fibroblasts incubated in a serum free medium[20].

VIP: VIP was found to stimulate proliferation of keratinocytes in the presence of lethally treated 3T3 fibroblast feeder cells and EGF, whereas substance P and CGRP were ineffective[67]. VIP stimulated adenylate cyclase activity in membranes obtained from cultured keratinocytes, indicating an involvement of cAMP as second messenger in this reaction. VIP and several inflammatory cytokines (Th-1 and 2) from mast cells and nerve endings are capable of inducing stem cell factor production from epidermal keratinocytes, a mechanism that could be involved in atopic dermatitis[68].

CGRP and PAR-2 agonists: CGRP appears to lead to a reduction of contact hypersensitivity by inducing mast cells to degranulate and thus release TNF-α and, most likely, IL-10[69]. CGRP, like α-MSH, down-regulates costimulatory molecule expression on dendritic cells in vitro and via the generation of suppressor T-lymphocytes to induce hapten specific tolerance in vivo[28]. PAR-2 agonists were found to induce the release of CGRP mediating vasodilation, plasma extravasation as well as the expression of adhesion molecules on vascular endothelial cells and thus elicit neurogenic inflammation. New evidence suggests that the release of neuropeptides, including CGRP, from cutaneous sensory c-fibers after UV radiation is induced by keratinocyte-derived nerve growth factor[69].

Serotonin: The relationship between function and serotonin receptor type is complex. Detection of 5HT1A, 5HT1B, 5HT2B and 5HT7 receptors on melanocytes and dermal fibroblasts is consistent with a putative function for serotonin as growth factor[70]. Serotonin stimulates proliferation of melanocytes in a medium deprived of growth factors, while it inhibits cell growth in the presence of growth factors[20].

Substance P: Substance P is released from cutaneous nerve fibers or mast cells in the extracellular space or at the cell surface to induce inflammatory or immune responses. SP promotes both the proliferation and the differentiation of sebaceous glands[71]. Mast cell-derived IL-6 and TNF-α, followed by SP-stimulated degranulation, have the potential to induce nerve growth factor expression by sebaceous cells, which results in the promotion of innervation and in the expression of E-selectin, respectively. Recently, undifferentiated germinative sebocytes were shown to produce high amounts of neutral endopeptidase in order to inactivate substance P in vitro and in acne-involved sebaceous glands in vivo[72].

GH and IGF-I: The effects of the GH/IGF-I axis result in a homeostatic regulation of cell proliferation and differentiation. GH activity is mainly mediated by the IGFs but GH also has direct effects on human skin cells[5]. GH enhances androgen effects on hair growth and is likely to be involved in sebaceous gland development. It stimulates sebocyte differentiation and also augments the effect of 5α-DHT on sebaceous lipid synthesis[73]. On the other hand, GH does not affect keratinocyte or sebocyte proliferation though it enhances the proliferation of dermal fibroblasts in vitro[29,73]. IGF-I and insulin have been shown to significantly stimulate sebocyte proliferation but also influence sebocyte differentiation, especially in combination with GH, in vitro[73,74]. Insulin may act as an IGF-I surrogate as it exhibits marked homology to the IGFs and binds the IGF-I receptor at high concentrations. IGF-I was also shown to promote clonal proliferation of cultured keratinocytes[29] and to up-regulate hyaluroran synthesis in dermal fibroblasts, exhibiting a similar effect to basal fibroblast growth factors[75]. GH and IGF-I induce increases in skin IGF-binding protein-3 mRNA abundance[76] with a magnitude dependent on the presence of Ca^{2+}. IGF-I at physiological levels is essential for hair follicle growth by preventing them from entering the catagen phase[77]. IGF molecules circulate mostly bound to IGF-binding proteins. The GH / IGF-I axis shows an age-related decreased hormone production concomitant with symptoms similar to those of GH-deficient adults[78]. Finally, GH is able to switch the predominant CRH receptor-1 mRNA expression to a sole CRH receptor-2 mRNA expression in human sebocytes[13], indicating a possible interaction of the GH/IGF-I axis with the hypothalamic-pituitary-adrenal axis in human skin. Skin is a target organ for GH in children; growth hormone increases dermal thickness and reduces skin stiffness in growth hormone-deficient children[79]. The IGF-I / IGF-I recep-

tor loop was found to be critically involved in maintenance of human skin organ cultures ex vivo[30]; IGF-I locally produced by dermal fibroblasts interacted in a paracrine manner with its receptor, predominantly expressed in basal keratinocytes, to maintain tissue homeostasis.

Thyroid hormones: Hypothyroidism causes disturbances of skin quality and hair character and growth with an increased telogen rate and diffuse alopecia[5,6]. Replacement reestablishes the normal anagen/telogen ratio. L-Triiodothyronine was shown to stimulate proliferation of outer root sheath keratinocytes and dermal papilla cells[80].

Androgens: The biological activity of testosterone on the skin is induced in large part by its conversion to 5α-DHT by 5α-reductase[81,82]. Testosterone and 5α-DHT, being the tissue active androgens, stimulate 5α-reductase mRNA and 5α-reductase activity and their effects are mediated through their binding to the AR. They stimulate proliferation of target cells, such as sebocytes and dermal papilla cells[83-86]. In addition, there is evidence that the effect of androgens on human sebocyte proliferation depends on the area of skin from which the sebaceous glands are obtained; facial sebocytes are mostly affected[83,87]. Androgens as single compounds seem to be unable to modify sebocyte differentiation[56], which is stimulated by co-incubation with PPARγ ligands[88]. Dermal papilla cells mediate the growth-stimulating signals of androgens by releasing growth factors that act in a paracrine fashion on the other cells of the follicle[5,86]. Excessive amounts of tissue active androgens were shown to induce apoptosis of dermal papilla cells through the bcl-2 pathway[89]. In aged skin, lower serum levels of testosterone and gradual decline in DHEA and DHEA sulfate are detected, at least in males[78]. Unexpectedly, testosterone has been reported to perturb epidermal permeability barrier homeostasis.[90]

Estrogens: For many years it has been recognized that estrogens are important in the maintenance of human skin[91]. They improve collagen content and quality, increase skin thickness and enhance vascularization, features highlighted by the changes that occur in the skin of postmenopausal women[92]. They have been shown to increase mitotic activity in the epidermis of women[93]. Estrogens prolong the growth period of scalp hair by increasing cell proliferation rates and postponing the anagen-telogen transition[86]. In parallel, 17α-estradiol, as a therapeutic compound, induces aromatase activity in intact human anagen hair follicles ex vivo.Under the influence of 17α-estradiol, an increased conversion of testosterone to 17β-estradiol and androstendione to estrone takes place, which might explain the beneficial effects of estrogen treatment of androgenic alopecia[94]. 17β-Estradiol exerts anti-inflammatory activity by inhibiting the chemokine RANTES and an interferon-γ-induced 10 kDa protein produced in human keratinocytes[95,96]. On the other hand, estrogens directly suppress an enhanced sebaceous gland function[12,97]. Both testosterone and estradiol are able to regulate CRH receptor mRNA levels in sebocytes, through an opposite way [13]. Estradiol has also been shown to increase proliferation of melanocytes but decrease both the melanin content and the tyrosinase activity[98]. Inhibition of 5α-reductase and of AR activity resulted in a great stimulation of vascular endothelial growth factor (VEGF) and aromatase expression in dermal papilla cells. Strong stimulation of VEGF protein and gene expression was also observed in the presence of 17β-estradiol[37]. Rapid potentiation of endothelium-dependent vasodilation by 17β-estradiol in postmenopausal women is mediated via cyclooxygenase 2[99]. There is current evidence that although skin cells express estrogen receptors making them directly susceptible to estrogens, a cross-talk between estrogen and IGF-I signaling pathways obviously takes place. IGF-I plays a major role in regulating lipid synthesis in sebocytes and proliferation in fibroblasts and may, therefore, mediate the estrogen activity in normal and aged skin cells[100]. On the other hand, phytoestrogens, such as genistein, probably regulate sebocyte differentiation through up-regulation of PPARγ expression[56].

Glucocorticoids: Glucocorticoids induce hair growth[101], stimulate sebocyte proliferation[74] and induce skin atrophy, probably due to an effect on dermal fibroblasts[102]. The aggravation of sebaceous gland diseases by glucocorticoids may be due to their stimulatory effects on proliferation and differentiation in the presence of other growth factors[12]. Glucocorticoids can regulate keratinocyte differentiation by repressing the expression of the basal cell specific keratins K5 and K14 and disease-associated keratins K6, K16, and K17, an effect induced directly through interactions of keratin response elements with glucocorticoids, and indirectly by blocking the AP-1 induction of keratin gene expression[103].

Retinoids: Retinoic acids exhibit earlier and stronger biological effects on the keratinocytes than retinol, probably due to their early high cellular accumulation and their less rapid metabolism[104,105]. These findings substantiate the assumption that the intensity of retinoid signaling is dependent, in part, on the quantity of cellular retinoic acid. This assumption is supported by the tight autoregulatory mechanism in human keratinocytes offering protection against excessive accumulation of cellular retinoic acid[49]. all-*trans* Retinoic acid binds to and induces cellular retinoic acid-binding protein II as well as binding to and activating nuclear RARs[106]. Most actions of all-*trans* retinoic acid are now recognized to be mediated through activation of RARs, whereas in epithelial skin cells, RAR modulate cell proliferation and RXR rather than influence cell differentiation[51]. Retinoids regulate proliferation and differentiation of skin epithelial cells towards a homeostatic status[105] notably inhibiting proliferation and lipogenesis in human sebocytes but enhancing these processes under vitamin A deficient conditions[107,108].

Vitamin D: 1α,25$(OH)_2D_3$ (calcitriol), the hormonal form of vitamin D, like retinoids, rapidly up-regulates the major vitamin D_3 (cholecalciferol) metabolizing enzyme 25-hydroxylase at the mRNA level, which is an established indicator for calcitriol presence[109]. It enhances the growth-promoting activity of autocrine EGF receptor ligands in keratinocytes[110] and can also rapidly increase the activity of 17β-hydroxysteroid dehydrogenase (isotype 2), which leads predominantly to conversion of estradiol to estrone[111]. This estradiol inactivation is enhanced with increasing calcitriol levels, which exhibit an antiproliferative effect on keratinocytes. This effect, which is mediated through TGF-β activation as well as IL-1α, IL-6 and IL-8 suppression, may provide a rationale for the beneficial effects of calcitriol and synthetic analog in the treatment of hyperproliferative skin disorders, whereas stimulatory effects through the EGF-related family members and platelet-derived growth factor may be operative in their beneficial effects in skin atrophy and wound healing[112]. The antiproliferative and anti-inflammatory effects of calcitriol in skin are also mediated, at least in part, by a complex TGF-β regulation in dermal fibroblasts[113]. Calcitriol also elicits the complete differentiative program in vitro, with expression of various genes/proteins, especially of protein kinase C and phospholipase D, characteristic of both early and late differentiation of keratinocytes[114]. In addition to its effects on keratinocyte proliferation and differentiation, calcitriol has been shown to protect keratinocytes from ultraviolet light- and chemotherapy-induced damage by inhibition of stress-activated protein kinases activation[115]. On the other hand, in vitro and in vivo experiments have shown that VDR ligands induce dendritic cells to acquire tolerogenic properties that favor the induction of regulatory rather than effector T cells[116].

Leptin: Leptin is a keratinocyte acting in vitro, and during skin repair in vivo, through a cytoplasmic activation of the signal transcription factor STAT-3[117]. In addition, leptin exhibits a proangiogenic activity probably through a bcl-2 dependent anti-apoptotic action on microvascular endothelial cells[118].

PPAR ligands: PPARs are pleiotropic regulators of growth and differentiation of many cell types, including skin cells. PPARα seems to contribute to skin barrier function and to regulation of inflammation, PPARγ is necessary for keratinocyte and sebocyte differentiation, and PPARδ can ameliorate inflammatory responses in the skin[55]. PPARδ is the predominant subtype in human keratinocytes and is highly expressed in basal and suprabasal cells[119,120]. Induction of PPARα and PPARγ expression is linked to differentiation and, accordingly, their expression is in essence confined to suprabasal cells[120]. PPARδ and PPARγ inhibition resulted in a dramatic decrease in proliferation and a robust up-regulation of the expression of involucrin and transglutaminase[120,121]. PPARs are expressed in the human sebaceous gland[56,122,123]. Linoleic acid, a natural PPARδ ligand, induces accumulation of neutral lipids in undifferentiated human sebocytes and reduces spontaneous IL-8 secretion[124]. Estradiol metabolizes prostaglandin Δ2 to Δ12-prostaglandin J2, a natural ligand for PPARγ[125], whereas the expression of PPARγ is up-regulated by the phytoestrogen genistein[56].

Eicosanoids: Proinflammatory cytokines, such as IL-1β and TNF-α, induce cytosolic phospholipase A_2 expression in keratinocytes and are able to increase the release of arachidonic acid and stimulate eicosanoid synthesis[126]. IL1α expression has been detected in follicular keratinocytes and sebocytes in vivo and in vitro[74,126-128]. Enhanced keratinocyte prostaglandin synthesis after UV light injury is also due to increased phospholipase activity[129]. The major arachi-

donic acid metabolites in skin cells are prostaglandin E_2 and leukotriene B_4 (LTB_4)[130], while TNF-α stimulates hydroxyeicosatetranoic acid (HETE) production. Interestingly, LTB_4 is a natural ligand for PPARα[131-133], soluble 15-HETE, which is a natural ligand for PPARγ[134] and is synthesized in human sebaceous glands[135], and PPARs can regulate lipid and lipoprotein metabolism, cell proliferation, differentiation and apoptosis of various cell types including sebocytes[88,133]. The axis arachidonic acid/LTB_4/PPARα/lipid synthesis and inflammation in human skin (Figure 2) was confirmed by a recent clinical study demonstrating that treatment of acne patients with zileuton, a selective 5-lipoxygenase inhibitor administered systemically, led to a 70% reduction in inflammatory acne lesions at 3 months and an approximately 65% reduction in total sebum lipids as well as a substantial decrease in proinflammatory lipids[136].

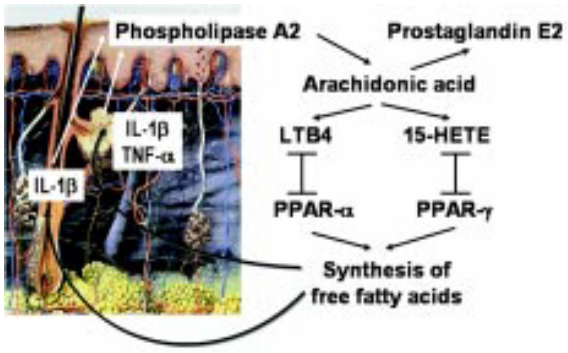

Figure 2. The cascade of eicosanoid synthesis and their PPAR-binding in human skin. IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; LTB4, leucotriene B4; 15-HETE, 15-hydroxyeicosatetranoic acid; PPAR-α, peroxisome proliferator-activated receptor-α; PPAR-γ, peroxisome proliferator-activated receptor-γ.

THE HUMAN SKIN AS ENDOCRINE GLAND

Hormone Synthesis in Human Skin

All types of small molecules can practically represent precursors of skin hormones which may be proteins, including glycoproteins, smaller peptides or peptide derivatives, amino acid analogs or lipids (Figure 3).

PTHrP: Keratinocytes produce abundant PTHrP which is down-regulated by calcitriol, suggesting a physiological role[137]. In addition, PTHrP is widely expressed in melanocytic cells; however, these cells do

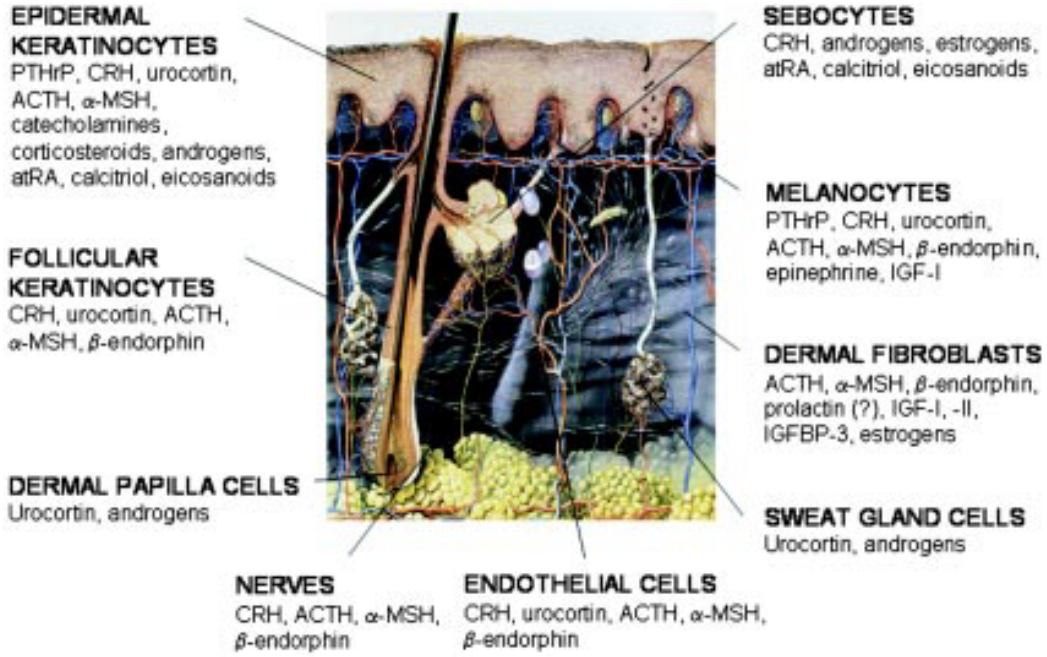

Figure 3. Synthesis of hormones in human skin. PTHrP, parathyroid hormone-related peptide; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; α-MSH, α-melanocyte-stimulating hormone; atRA, all-*trans* retinoic acid; IGF-I, insulin-like growth factor-I; IGF-II, insulin-like growth factor-II; IGFBP3, insulin-like growth factor-binding protein-3.

not secrete PTHrP[138].

CRH and urocortin: CRH, modified amino acid as well as CRH binding protein are expressed in human sebocytes at the mRNA and protein levels[13] and have also been detected in epidermal and follicular keratinocytes, melanocytes, endothelial cells and dermal nerves but not in fibroblasts[12].

The gene of the CRH-related urocortin, a ligand of CRH-2 receptor, and accumulation of the corresponding peptide have been detected in human skin cells[139]. Urocortin antigen has been localized to epidermal and follicular keratinocytes and sweat glands, epidermal melanocytes, blood vessels walls, dermal smooth muscle, mononuclear inflammatory cells and dermal fibroblasts.

POMC peptides: POMC mRNA is expressed in melanocytes[18]. POMC cleavage products, such as ACTH, MSH isotypes and β-endorphin, are produced in several skin cell types in vivo and in vitro[12,14,140]. ACTH and α-MSH are mainly expressed in epidermal keratinocytes, melanocytes, the outer root sheath of the anagen hair follicle, dermal fibroblasts and microvascular endothelial cells. β-Endorphin is mainly produced by the outer root sheath of the anagen hair follicle and dermal fibroblasts.

Prolactin: Recent data on prolactin synthesis in human skin are controversial. While dermal fibroblasts in vitro were shown to synthesize prolactin in one study[141], no prolactin mRNA was detected in human skin in another study[142].

Catecholamines: Norepinephrine and epinephrine, which are modified amino acids and natural activators of the cAMP pathway, are produced in human keratinocytes but not in melanocytes[143].

IGF-I: Although there is no evidence that GH or GH-like peptides are produced in the skin, its downstream peptide, IGF-I, is synthesized in the skin, mainly by dermal fibroblasts and melanocytes and also possibly by keratinocytes of the stratum granulosum[29,144]. Dermal fibroblasts are also a source of IGF-II and IGF-binding protein-3[145,146].

Steroid hormones: The skin, especially the sebaceous glands, is capable of synthesizing cholesterol - from two-carbon fragments such as acetate[147,148] - which is utilized in cell membranes for the formation of the epidermal barrier, in sebum, and as substrate for steroid hormone synthesis in the skin, and especially in the sebaceous gland[149]. The local formation of sex steroids provides autonomous control to human skin which is thus able to adjust the formation and metabolism of sex steroids according to local needs[3,7,149]. The situation of a high secretion rate of adrenal precursor sex steroids in men and women is completely different from the animal models used in the laboratory (except monkeys), where the secretion of sex steroids takes place exclusively in the gonads. In these lower animal species, no significant amounts of androgens or estrogens are synthesized outside the testes or ovaries and no sex steroid is detected after castration. Sex steroids in human skin are activated intracellularly and exert their action within the cells without release in the extracellular space and in the general circulation (intracrine function)[7]. The rate of formation of each sex steroid thus depends upon the level of expression of each of the specific androgen- and estrogen-synthesizing enzymes in each cell type. Sebaceous glands and sweat glands account for the vast majority of androgen metabolism in skin[3,5].

Skin is also a source of corticosteroids[102].

Retinoids: In humans, vitamin A (retinol) and natural retinoids are derived from carotenoids in the diet that are modified by the body; in the skin, excess retinol is mainly esterified[106,150]. Human keratinocytes in vitro are able to produce low amounts of the intracellularly active metabolite all-*trans* retinoic acid[104,105,151].

Vitamin D: The skin is the unique site of cholecalciferol synthesis[152,153] which, like steroid hormones, derives from cholesterol. Epidermal keratinocytes contain both the mechanism needed to produce calcitriol and VDR[116].

Eicosanoids: Eicosanoids, such as prostaglandins, prostacyclins and leukotrienes, are fatty acid derivatives. Eicosanoid synthesis can also be induced in human keratinocytes and sebocytes by several proinflammatory signals[129,130,154].

Activation and Inactivation of Hormones in Human Skin

In addition to its capacity to produce hormones, the human skin is able to metabolize hormones in order to activate or inactivate them. These metabolic steps are undertaken in most cases by different skin cell populations in a coordinated way, indicating the

endocrine autonomy of the skin. Characteristic examples of this kind of endocrine skin function are the metabolic pathways of the CRH / POMC axis, sex steroids, vitamin D and retinoids.

The CRH/POMC axis: The skin is strategically located as a barrier between the external and internal environments being permanently exposed to noxious stressors. To effectively deal with such damaging signals, the skin exhibits a highly organized CRH / POMC system which is analogous to the hypothalamic-pituitary-adrenal axis and is a major stress response system[12]. Activation of this pathway by stress-sensoring cutaneous signals, mainly proinflammatory cytokines, proceeds through the production and release of CRH from keratinocytes, melanocytes, endothelial cells and dermal nerves which stimulate skin cell CRH receptors in a paracrine and autocrine manner. CRH synthesis in melanocytes is up-regulated by ultraviolet radiation B and down-regulated by dexamethasone[12]. Interestingly, CRH receptors in human sebocytes can be regulated by several other downstream hormones, mainly by testosterone, estrogens and GH[13]. CRH enhances the production and secretion of the POMC peptides α-MSH, ACTH, and β-endorphin, especially in keratinocytes, melanocytes, endothelial cells and cutaneous nerves[14,140] by a complex multistep process that requires POMC processing by prohormone convertases[12]. These enzymes are expressed in keratinocytes, melanocytes and endothelial cells. Production of α-MSH and ACTH can be significantly upregulated by ultraviolet light and IL-1 and down-regulated by TGF-β and dexamethasone. ACTH activates the steroidogenic acute regulatory protein and thus the MC receptors inducing, thereby, the production and secretion of cortisol[155], a powerful natural anti-inflammatory factor that counteracts the effect of stress signals and buffers tissue damage.

Steroidogenesis: Human sebocytes and keratinocytes express the steroidogenic acute regulatory protein which is essential for cholesterol translocation from the outer to the inner mitochondrial membrane and thus the initiation of steroidogenesis[149] (Figure 4). They also express P450 side chain cleavage enzyme which catalyses the conversion of cholesterol into pregnenolone, cytochrome P450 17-hydroxylase that leads to precursors of cortisol and DHEA, and steroidogenic factor-1 which maintains these reactions. DHEA can be further converted into androstenedione and the tissue potent androgen testosterone by sebocytes and dermal papilla cells since they express 3β-hydroxysteroid dehydrogenase-Δ^{5-4} isomerase[3,156,157]. Further activation of testosterone by its conversion into 5α-DHT is catalyzed by 5α-reductase type 1 which is expressed in almost all skin cells but especially in sebocytes[81], while fibroblasts and dermal papilla cells also express 5α-reductase type 2[37]. Sebocytes are also able to regulate the balance of testosterone and androstenedione bidirectionally by expressing the 17β-hydroxysteroid dehydrogenase isotypes 2 and 3[3]. Androgen conversion to estrogens in the skin takes place in dermal fibroblasts which express the responsible enzyme cytochrome P450 19 (aromatase), and androgen inactivation to androsterone or 3α-androstanediol in epidermal keratinocytes which strongly express the responsible enzyme 3α-hydroxysteroid dehydrogenase[3,158]. In contrast to this skin-related pathway, conversion of the adrenal DHEA sulfate - which reaches the skin through the circulation - to DHEA occurs with the assistance of dermal papilla cells and monocytes which exhibit steroid sulfatase activity[156,157,159]. Therefore, the skin is a steroidogenic tissue and different skin cell types exert distinct duties in the synthesis of tissue active androgens and their inactivation leading to androgen and estrogen homeostasis. Adrenal androgens may only be activated in the skin in pathologic conditions which require the presence of inflammatory cells in the skin.

In addition, evaluation of skin layer-specific prednicarbate biotransformation has shown that epidermal keratinocytes can hydrolyze the double ester prednicarbate at position 21 to the monoester prednisolone 17-ethylcarbonate which nonenzymatically transforms to prednisolone 21-ethylcarbonate. This metabolite is enzymatically cleaved to prednisolone, the main biotransformation corticosteroid product. Fibroblasts show a distinctively lower enzyme activity[102]. Prednicarbate, prednisolone 17-ethylcarbonate and prednisolone 21-ethylcarbonate are hydrolyzed to a minor extent only. Therefore, epidermal keratinocytes are likely to be responsible for the conversion of potent corticosteroids to less potent ones in human skin, while dermal fibroblasts are barely able to metabolize the steroids.

The retinoid pathway: Epidermal keratinocytes in vivo regulate the levels of the intracellularly active all-*trans* retinoic acid by induction of retinoic acid 4-hy-

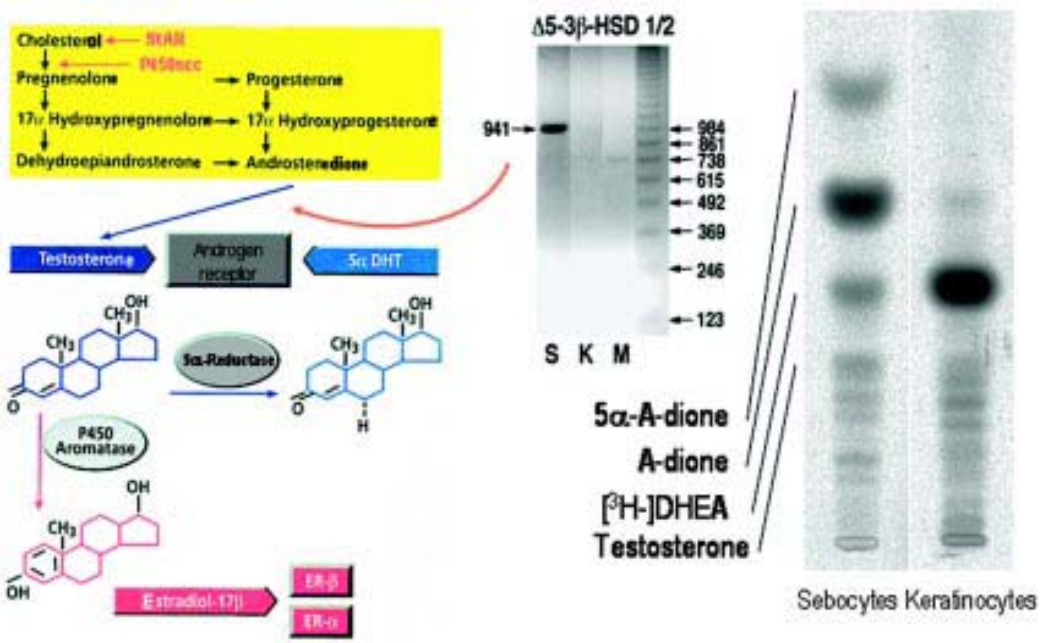

Figure 4. Steroidogenesis in human skin. *Left panel:* The complete pathway of sex hormone synthesis from cholesterol. StAR, steroidogenic acute regulatory protein; P450scc, cytochrome P450 side chain cleavage enzyme; 5α-DHT, 5α-dihydrotestosterone; ER, estrogen receptor. *Middle panel:* Sebocytes (S), but neither keratinocytes (K) nor melanocytes (M), express 3β-hydroxysteroid dehydrogenase-Δ^{5-4}-isomerase (Δ5-3β-HSD), the enzyme converting dehydroepiandrosterone and androstenedione to testosterone at the mRNA level (RT-PCR). *Right pannel:* Sebocytes but not keratinocytes are able to metabolize ^{3}H-dehydroepiandrosterone ([^{3}H-]DHEA) to downstream androgen compounds.

droxylase[160]. atRA inactivation by 4-hydroxylation prevents endogenous and exogenous all-*trans* retinoic acid accumulation in the epidermis. In contrast to all-*trans* retinoic acid, retinol, retinaldehyde, 9-*cis* retinoic acid and 13-*cis* retinoic acid are not able to regulate their own hydroxylation. In contrast, human keratinocytes in vitro rapidly take up and initially convert retinol to retinyl esters and then with time to low amounts of the intracellularly active metabolite all-*trans* retinoic acid[104,105,151]. 3,4-Didehydro-retinol can also be detected[105,160]. However, ester formation, especially of retinyl oleate (18:1) and retinyl palmitate (16:0), remains the main root by which excess retinol is also handled by human keratinocytes in vitro[104,105,151,161]. Retinoid metabolism in human skin is likely to be a cell-specific event since sebocytes exhibit a distinct metabolic pattern compared to epidermal keratinocytes[51].

The vitamin D pathway: The skin is the unique site of cholecalciferol production and the liver is thought to be the main site of conversion to 25(OH)D_3. The skin is further capable of activating 25(OH)D_3 via 1α-hydroxylation and the resulting calcitriol plays a role in epidermal homeostasis in normal and diseased skin. Human keratinocytes have been shown to substantially but slowly convert ^{3}H-D_3 to ^{3}H-25(OH)-D_3[109]. In addition, they were found to slowly but constantly form calcitriol from a large reservoir of cholecalciferol. Interestingly, physiological doses of ultraviolet light B radiation at 300 nm induce the conversion of 7-dehydrocholesterol via pre-cholecalciferol and cholecalciferol into calcitriol in the pmol range in epidermal keratinocytes[153]. Skin can further degrade cholecalciferol: Cytochrome P450 27 in epidermis completes the set of essential cholecalciferol hydroxylases[109]. Thus, by orchestrating the entire system of production, activation and inactivation, skin is an autonomous source of hormonally active calcitriol.

Release of Skin Hormones in the Circulation

There is increasing evidence that human skin produces hormones which are released in the circulation

and are important for functions of the entire human organism[162]. For example, IGF-binding protein-3 message abundance is greater in the skin than in the liver and circulating IGF-binding protein-3 concentrations are significantly increased by GH and IGF-1[76]. GH has a direct effect on the regulation of IGF-binding protein-3 synthesis, and the response of skin IGF-binding protein-3 mRNA levels to both GH and IGF-I suggests that dermal fibroblasts could be more important than the liver in the regulation of the circulating reservoir of IGF-binding protein-3 in certain circumstances.

A large proportion of androgens and estrogens in men and women are synthesized locally in the skin from the inactive adrenal precursors DHEA and androstenedione. DHEA and androstenedione are converted to testosterone and further to 5α-DHT by the intracellular enzyme 5α-reductase in skin, thus making the skin a source of considerable amounts of the circulating testosterone and 5α-DHT levels. Circulating testosterone is co-produced in the skin and in other peripheral organs[8]. The best estimate of the intracrine formation of estrogens in peripheral tissues in women is in the order of 75% before menopause and close to 100% after menopause, except for a small contribution from ovarian and/or adrenal testosterone and androstenedione[7]. Thus, in postmenopausal women, almost all active sex steroids are made in target tissues by an intracrine mechanism.

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