Human Skin: An Independent Peripheral Endocrine Organ

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Abstract
The historical picture of the endocrine system as a set of discrete hormone-producing organs has been substituted by organs regarded as organized communities in which the cells emit, receive and coordinate molecular signals from established endocrine organs, other distant sources, their neighbors, and themselves. In this wide sense, the human skin and its tissues are targets as well as producers of hormones. Although the role of hormones in the development of human skin and its capacity to produce and release hormones are well established, little attention has been drawn to the ability of human skin to fulfil the requirements of a classic endocrine organ. Indeed, human skin cells produce insulin-like growth factors and -binding proteins, propiomelanocortin derivatives, catecholamines, steroid hormones and vitamin D from cholesterol, retinoids from diet carotenoids, and eicosanoids from fatty acids. Hormones exert their biological effects on the skin through interaction with high-affinity receptors, such as receptors for peptide hormones, neurotransmitters, steroid hormones and thyroid hormones. In addition, the human skin is able to metabolize hormones and to activate and inactivate them. These steps are overtaken 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. Hormones exhibit a wide range of biological activities on the skin, with major effects caused by growth hormone/insulin-like growth factor-1, neuropeptides, sex steroids, glucocorticoids, retinoids, vitamin D, peroxisome proliferator-activated receptor ligands, and eicosanoids. At last, human skin produces hormones which are released in the circulation and are important for functions of the entire organism, such as sex hormones, especially in aged individuals, and insulin-like growth factor-binding proteins. Therefore, the human skin fulfils all requirements for being the largest, independent peripheral endocrine organ.

Introduction

The human skin is the target for a wide range of chemical messengers. These include several hormones, which in the classical sense are defined as substances secreted into

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the blood stream by specific ductless glands. Their effects have long been recognized and in some instances well characterized. For example, hair follicles and sebaceous glands are the targets for androgen steroids secreted by the gonads and the adrenal cortex [1, 2] and melanocytes are directly influenced by polypeptide hormones of the pituitary [3]. However, the historical picture of the endocrine system as a set of discrete hormone-producing organs, most of them under the control of a master gland, the pituitary, has become extended and modified to the point of metamorphosis. The skin and other tissues can no longer be regarded simply as the recipients of signals from distant transmitters. They must rather be viewed as organized communities in which the cells emit, receive and coordinate molecular signals from a seemingly unlimited number of distant sources in addition to the established endocrine organs (modern and classic endocrine functions, respectively), their neighbors (paracrine and juxtacrine function), and themselves (autocrine and intracrine function) (fig. 1). In the widest sense the human skin and its tissues are thus the targets as well as the producers of hormones.

In addition to the modified determination of the endocrine skin functions, the results of current research have blurred the distinction between hormones secreted into the blood stream and locally active factors. Epithelial skin cells share common properties with secretory neurons exhibiting a complete hypothalamic-pituitary-like axis [4] and the skin converts the circulating androgen steroids dehydroepiandrosterone (DHEA) and androstenedione to testosterone and further to 5α-dihydrotestosterone (5α-DHT) by the intracellular enzyme 5α-reductase but is also responsible for large amounts of the circulating testosterone and 5α-DHT levels [2, 5]. Finally, the identification of a number of pharmacologically active peptides in a range of tissues throughout the body focused attention on the ubiquity of locally acting hormones.

Although the role of hormones in the development of human skin tissues and their capacity to produce and release further hormones are well established [6, 7], little attention has been drawn to the ability of human skin to fulfil the requirements of a classic endocrine organ, namely synthesis of hormones from major classes of compounds used by the body for general purposes, binding and regulation of specific receptors by the derived hormones, 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.
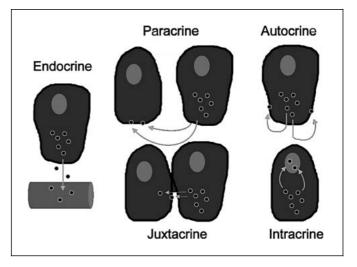

Fig. 1. Modes of hormone action. Classical and modern endocrine functions: Hormones produced by established endocrine organs or other distant sources, respectively, reach target tissues through the circulation. Paracrine function: Hormones act locally on cells other than those that produce them. Juxtacrine function: Hormones produced in one cell interact directly with a receptor of an immediate neighboring cell. Autocrine function: Hormones act on the cell in which they are produced. Intracrine function: Hormones get activated in the cell in which they are produced and act on it by binding to nuclear receptors.
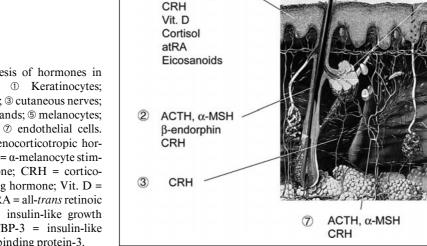
Synthesis of Hormones in Human Skin

All types of small molecules can practically represent precursors of skin hormones which can be proteins, including glycoproteins, smaller peptides or peptide derivatives, amino acid analogs or lipids (fig. 2).

Polypeptide hormones are direct translation products of specific mRNA, such as growth hormone (GH), and cleavage products of large precursor proteins, such as pro-piomelanocortin (POMC) derivatives and prolactin. Although there is no evidence that GH or GH-like peptides are produced in the skin, its downstream peptide, insulin-like growth factor-I (IGF-I), is synthesized in the skin, mainly by dermal fibroblasts and melanocytes and also possibly by keratinocytes of the stratum granulosum [8, 9]. Dermal fibroblasts are also source for IGF-II and IGF-binding protein (IGFBP)-3 [10, 11].

POMC derivatives, such as adrenocorticotropic hormone (ACTH), melanocyte stimulating hormone (MSH) isotypes and β-endorphin are produced in several skin cell types in vivo and in vitro [4, 12–15]. ACTH and α-MSH are mainly expressed in epidermal keratinocytes, melanocytes, the outer root sheath of the anagen hair follicle,

Fig. 2. Synthesis of hormones in human skin. ① Keratinocytes; ② hair follicles; ③ cutaneous nerves; ④ sebaceous glands; ⑤ melanocytes; ⑥ fibroblasts; ⑦ endothelial cells. ACTH = Adrenocorticotropic hormone; α-MSH = α-melanocyte stimulating hormone; CRH = corticotropin releasing hormone; Vit. D = vitamin D; atRA = all-*trans* retinoic acid; IGF-I = insulin-like growth factor I; IGFBP-3 = insulin-like growth factor binding protein-3.

dermal fibroblasts and microvascular endothelial cells. β-Endorphin is mainly produced by the outer root sheath of the anagen hair follicle and dermal fibroblasts.

The few data existing on prolactin synthesis in human skin are controversial. While dermal fibroblasts in vitro have been shown to synthesize prolactin [16], no prolactin mRNA was detected in human skin in another study [17].

Catecholamines – norepinephrine and epinephrine – which are modified amino acids and natural activators of cAMP pathway, are produced in human keratinocytes but not in melanocytes [18]. Another type of modified amino acid, the corticotropin releasing hormone (CRH), has been detected in epidermal and follicular keratinocytes, melanocytes, endothelial cells, and dermal nerves but not in sebocytes or fibroblasts [4, 19].

Steroid hormones and vitamin D are derived from cholesterol. The skin, especially the sebaceous glands, is capable of synthesizing cholesterol – from two-carbon fragments such as acetate [20, 21] – which is utilized in cell membranes, formation of the epidermal barrier, in sebum, and as substrate for steroid hormone synthesis [22]. Skin is also source of corticosteroids [23] and the unique site of vitamin D_3 (cholecalciferol) production [24, 25].

Retinoids and eicosanoids, such as prostaglandins, prostacyclins and leukotrienes, are fatty acid derivatives. 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 [26]. Human keratinocytes in vitro are able to produce low amounts of the intracellularly active metabolite all-*trans* retinoic acid (atRA) [27–29]. Eicosanoid synthesis can also be induced in human keratinocytes by several proinflammatory signals [30, 31].

Hormone Receptors in Human Skin

Hormones exert their biological effects on the skin through interaction with high-affinity receptors, which are, in turn, linked to one or more effector systems within cells. These effectors involve many different components of the cellular metabolic machinery, ranging from ion transport at the cell surface to stimulation of the nuclear transcriptional apparatus. In general, receptors for the peptide hormones and neurotransmitters are aligned on the cell surface, while those for the steroid and thyroid hormones are found in the cytoplasmic or nuclear compartments.

Receptors for the Peptide Hormones and Neurotransmitters

The peptide hormone and neurotransmitter receptors fall into four major groups; three of them are represented in human skin. The first includes the so-called serpentine or 'seven transmembrane domain' receptors which contain an amino terminal extracellular domain followed by seven hydrophobic amino acid segments, each of which is believed to span the membrane bilayer. The seventh segment is followed by a hydrophilic carboxyl terminal

domain that resides within the cytoplasmic compartment. To this group belong the parathyroid hormone (PTH)/parathyroid hormone-related peptide (PTHrP) receptor which is expressed in dermal fibroblasts but not in epidermal keratinocytes [32, 33], the thyroid-stimulating hormone (TSH) receptor which is present in dermal fibroblasts [34], the CRH receptors from which type 1 is present in epidermal and follicular keratinocytes, melanocytes, and dermal fibroblasts, whereas sebocytes express types 1 and 2 [4, 19], the melanocortin receptors (MCR), among them MCR1 which presents high affinity for α-MSH and 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, MCR2 which is specific for ACTH and is expressed in epidermal melanocytes and adipocytes, and MCR5 which shows affinity for α-MSH and ACTH and is present in sebocytes, sweat gland cells and adipocytes [4, 12, 35, 36], the μ-opiate receptors which bind with high affinity β-endorphin and are expressed in epidermal and outer root sheat keratinocytes, undifferentiated sebocytes and cells of the sweat gland secretory portion [4], the vasoactive intestinal popypeptide (VIP) receptors which are expressed in epidermal keratinocytes, sebocytes, sweat gland cells, endothelial cells, mononuclear cells and dermal nerve fibers [37–39], the neuropeptide Y receptor which is present in sebocytes [38], and the calcitonin gene-related peptide (CGRP) receptor which is expressed in sebocytes and Langerhans cells [38, 40].

The second group includes the single-transmembrane domain receptors that harbor intrinsic tyrosine kinase activity. This includes the insulin/IGF-I receptor and the epidermal growth factor receptor which are expressed in epidermal keratinocytes [8, 41].

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 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 eccrine sweat gland secretory duct, hair matrix cells of the dermal papillae, endothelial cells, Schwann cells of peripheral nerve fascicles, and adipocytes of the dermis [8, 42, 43].

Steroid Hormone and Thyroid Hormone Receptors

The nuclear receptors differ from the receptors of the cell membrane in that they are soluble receptors with a proclivity for employing transcriptional regulation as a means of promoting their biological effects. Thus, though some receptors are compartmentalized in the cytoplasm while others are defined 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 based on shared structural and functional properties.

The first group, the steroid receptor family, includes the glucocorticoid receptor which is mainly expressed in basal keratinocytes, Langerhans cells and dermal fibroblasts [44, 45], the androgen receptor which is present in epidermal and follicular keratinocytes, sebocytes, sweat gland cells, dermal papilla cells, dermal fibroblasts, endothelial cells, and genital melanocytes [2, 46–48], and the progesterone receptor which is expressed in basal epidermal keratinocytes only [49]. The glucocorticoid receptor is down-regulated by its ligands in dermal fibroblasts but is not affected by aging [50, 51]. Steroid receptors under basal conditions exist as cytoplasmic, multimeric 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 the thyroid hormone receptors (isotypes α1 and β1), whereas the isotype β1 is present in epidermal keratinocytes, outer root sheat cells, cebocytes, dermal papilla cells, and dermal fibroblasts [6, 52, 53], the estrogen receptor-β (but not the estrogen receptor-α) which is expressed in dermal papilla cells and dermal fibroblasts, sebocytes, adipocytes, melanocytes, and keratinocytes of the outer root sheath [48, 54–56], 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 RXRα isotype is present in melanocytes, fibroblasts, and inflammatory cells [57–61], the vitamin D receptor which is present in keratinocytes of all epidermal layers except those of the stratum corneum, epithelial cells of the epidermal appendages, mela-

nocytes, Langerhans cells, CD11b+ macrophages and CD3+ T-lymphocytes [62, 63], and 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 [64]. The members of the thyroid receptor family share a high degree of homology to the proto-oncogene c-erbA 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 they 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. The estrogen receptor binds to its regulatory element as a homodimer, while the other receptors prefer binding as heterodimers together with a RXR molecule. The latter amplifies both the DNA binding and the functional activity of the receptor.

Activation and Inactivation of Hormones in Human Skin

In addition to its capacity to produce hormones and express receptors for binding of distant, paracrine, juxtacrine, autocrine, and intracrine hormones, the human skin is able to metabolize hormones in order to activate and inactivate them. These steps are overtaken in most cases by different skin cell populations in a coordinated way indicating the endocrine autonomy of the skin. Characteristic examples for 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 hypothalamus/pituitary/adrenal axis [4]. Activation of this pathway by stress-sensing cutaneous signals, mainly proinflammatory cytokines, proceeds through the production and release of CRH from keratinocytes, melanocytes, endothelial cells, and dermal nerves which stimulates skin cell CRH receptors in paracrine and autocrine manners. CRH synthesis in melanocytes is up-regulated by ultraviolet radiation B and down-regulated by dexamethasone [4]. Interestingly, CRH receptors in human sebocytes can be

regulated by several downstream hormones, mainly by testosterone, estrogens, and GH [19]. 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 [12, 13, 15] by a complex multistep process that requires POMC processing by prohormone convertases [4]. These enzymes are expressed in keratinocytes, melanocytes, and endothelial cells. Production of α-MSH and ACTH can be significantly up-regulated by ultraviolet light and interleukin (IL)-1 and down-regulated by tumor growth factor-β and dexamethasone. ACTH activates the steroidogenic acute regulatory protein and thereof the MCR inducing thereby the production and secretion of cortisol [65], 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 [22] (fig. 3). They also express the P450 side chain cleavage enzyme which catalyses the conversion of cholesterol into pregnenolone, the cytochrome P450 17-hydroxylase that leads to precursors of cortisol and DHEA, and the steroidogenic factor-1 which maintains these reactions. DHEA can be further converted into androstenedione and the tissue potent androgen testosterone by sebocytes only, since only sebocytes express 3β-hydroxysteroid dehydrogenase-Δ^{5-4} isomerase [2]. 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 [66], while fibroblasts and dermal papilla cells also express 5α-reductase type 2 [48]. Sebocytes are also able to regulate the balance of testosterone and androstenedione bidirectionally by expressing the 17β-hydroxysteroid dehydrogenase isotypes 2 and 3 [2]. 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 [2, 67]. In contrast to this skin-related pathway, conversion of the adrenal DHEA sulfate – which reaches the skin through the circulation – to DHEA only occurs with the assistance of monocytes which exhibit steroid sulfatase activity [68]. Therefore, the skin is a steroidogenic tissue and different skin cell types overtake distinct duties in the
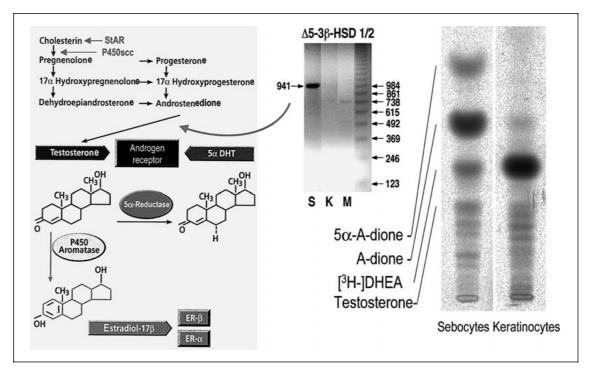
Fig. 3. Steroidogenesis in human skin. Left panel: The complete pathway of sex hormone synthesis from cholesterine. StAR = steroidogenic acute regulatory protein, P450scc = cytochrome P450 side chain cleavage enzyme, 5α-DHT = 5α-dihydrotestosterone, ER = estrogen receptor. Middle panel: Sebocytes (S) but neither keratinocytes (K) nor melanocytes (M) express 3β-hydroxysteroid dehydrogenase-Δ^{5-4}-isomerase ($\Delta5$–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.

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 [23]. 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 Vitamin D Pathway

Skin is the unique site of vitamin D_3 production and liver is thought to be the main site of conversion to $25(OH)D_3$. Skin is further capable of activating $25(OH)D_3$ via 1α-hydroxylation and the resulting $1\alpha,25(OH)_2D_3$ (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 [24]. In addition, they were found to slowly but constantly form calcitriol from a large reservoir of D_3. Interestingly, physiological doses of ultraviolet light B radiation at 300 nm induce the conversion of 7-dehydrocholesterol via pre-D_3 and D_3 into calcitriol in the picomolar range in epidermal keratinocytes [25]. Skin can further degrade vitamin D_3: Cytochrome P450 27 in epidermis completes the set of essential vitamin D_3 hydroxylases [24]. Thus, by orchestrating the entire system of production, activation and inactivation, skin is an autonomous source of hormonally active calcitriol.

The Retinoid Pathway

Epidermal keratinocytes in vivo regulate the levels of the intracellularly active all-*trans* retinoic acid (atRA) by induction of retinoic acid 4-hydroxylase [69]. atRA inactivation by 4-hydroxylation prevents endogenous and exogenous atRA accumulation in the epidermis. In contrast to atRA, retinol, retinaldehyde, 9-*cis* retinoic acid, and 13-*cis* retinoic acid are not able to regulate their own hydroxylation. On the other hand, 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 atRA [27–29]. 3,4-Didehydro-retinol can also be detected [27, 70]. 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 [27–29, 70]. Retinoid metabolism in human skin is likely to be a cell-specific event, since sebocytes exhibit a distinct metabolic pattern compared to epidermal keratinocytes [60].

Biological Activity of Hormones in Human Skin

GH and IGF-I

The effects of the GH/IGF-I axis are addressed towards a homeostatic regulation of cell proliferation and differentiation. GH activity is mainly mediated by the IGFs but GH has also direct effects on human skin cells [6]. 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 [71]. On the other hand, GH does not affect keratinocyte or sebocyte proliferation but it enhances the proliferation of dermal fibroblasts in vitro [8, 71]. IGF molecules circulate mostly bound to IGFBPs. GH and IGF-I induce increases in skin IGFBP-3 mRNA abundance [11], 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 [72]. IGF-I and insulin have been shown to significantly stimulate sebocyte proliferation but also influence sebocyte differentiation, especially in combination with GH, in vitro [71, 73]. 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 [8] and to upregulate hyaluroran synthesis in dermal fibroblasts exhibiting a similar effect to basal fibroblast growth factors [74]. The IGF-I/IGF-I receptor loop was found to be critically involved in maintenance of human skin organ cultures ex vivo [41]; IGF-I locally produced by dermal fibroblasts interacted in a paracrine manner with its receptor, predominantly expressed in basal keratinocytes, to maintain tissue homeostasis. The GH/IGF-I axis shows an age-related decreased hormone production concomitant with symptoms similar to those of GH-deficient adults [75]. At last, GH is able to switch the predominant CRH receptor-1 mRNA expression to a sole CRH receptor-2 expression in human sebocytes [19] indicating a possible interaction of the GH/IGF-I axis with the hypothalamus/pituitary-like axis in human skin.

Neuropeptides

POMC peptides are likely to play a major role in the regulation of skin pigmentary system [3, 76] and of cutaneous inflammation [12, 13]. ACTH and α-MSH exhibit the most significant melanogenic activity via cAMP-dependent pathways and tyrosinase activation, which is enhanced by ultraviolet light [4]. 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 tumor necrosis factor (TNF)-α-stimulated expression of the intracellular adhesion molecule-1. In keratinocytes, α-MSH stimulates cell proliferation and down-regulates expression of hsp 70 [77] and modulates cytokine production with up-regulation of IL-10 and inhibition of the IL-1-induced production and secretion of IL-8 [12, 13]. The latter effect was also detected in sebocytes and fibroblasts, where it may be mediated by NF-kB and AP-1 [35, 78]. β-Endorphin was shown to stimulate cytokeratin 16 expression and down-regulate μ-opiate receptor expression in human epidermis [79]. VIP, in the presence of lethally treated 3T3 fibroblast feeder cells and epidermal growth factor, stimulated proliferation of keratinocytes, whereas substance P and CGRP were ineffective. VIP stimulated adenylate cyclase activity in membranes obtained from cultured keratinocytes, indicating an involvement of cAMP as second messenger in this reaction [80]. On the other hand, it is likely that overproduction of ACTH may prolong the anagen phase of hair cycle [4]. α-MSH also stimulates synthesis and activity of collagenase/matrix metalloproteinase-1 in dermal fibroblasts [81]. TNF-α addition resulted in increased β-endorphin and ACTH levels [14]. In contrast, tumor growth factor-β-stimulated fibroblasts showed no

alteration in β-endorphin and α-MSH levels, whereas ACTH release was significantly enhanced. α-MSH may play a crutial role on endothelial cell function by decreasing the adherence and transmigration of inflammatory cells, a prerequisite for immune and inflammatory reactions [4]. The POMC peptides have strong immunomodulatory potential resulting in an overall immunosuppressive effect with α-MSH presenting the widest spectrum of activities [12], such as suppression of the contact hypersensitivity reaction to nickel by systemic or topical application [4]. Both α-MSH and β-endorphin induced histamine release from human foreskin mast cells in vitro [14].

Sex Steroids

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 [2, 82]. 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 made outside the testes or ovaries and no sex steroid is left after castration. Sex steroids in human skin are activated intracellularly and exert their action on the cells themselves without release in the extracellular space and in the general circulation (intracrine function). 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 [2, 6].

The biological activity of testosterone on the skin is effected in large part by its conversion to 5α-DHT by 5α-reductase [83]. 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 androgen receptor. They stimulate proliferation of target cells, such as sebocytes and dermal papilla cells [84–87]. 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 [84, 88]. Androgens have also been shown to stimulate sebocyte differentiation [89] which is augmented by co-incubation with PPARγ ligands [90]. Dermal papilla cells mediate the growth-stimulating signals of androgens by releasing growth factors that act in a para-

crine fashion on the other cells of the follicle [6, 87]. Excessive amounts of tissue active androgens were shown to induce apoptosis of dermal papilla cells through the bcl-2 pathway [91]. In aged skin, lower serum levels of testosterone and gradual decline in DHEA and DHEA sulfate are detected, at least in males [75].

Estrogens prolong the growth period of scalp hair by increasing cell proliferation rates and postponing the anagen-telogen transition [87]. On the other hand, they directly suppress an enhanced sebaceous gland function [4, 89]. Estradiol has also been shown to increase proliferation of melanocytes but decrease both the melanin content and the tyrosinase activity [56]. Inhibition of 5α-reductase and of androgen receptor 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 [48]. Both testosterone and estradiol are able to regulate CRH receptor mRNA levels, whereby in an opposite way [19].

Glucocorticoids

Glucocorticoids induce hair growth [92], stimulate sebocyte proliferation [73], and induce skin atrophy probably due to an effect on dermal fibroblasts [23]. 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 [4]. 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 [93].

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 [29, 94]. These findings support 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 [58]. atRA binds to and induces cellular retinoic acid-binding protein II (CRABP II) as well as binds to and activates nuclear RARs [95]. Most actions of atRA are now recognized to be mediated through activation of RARs,

whereas, in epithelial skin cells RAR modulate cell proliferation and RXR rather influence cell differentiation [60]. Retinoids regulate proliferation and differentiation of skin epithelial cells towards an homeostatic status [94], especially inhibit enhanced proliferation and lipogenesis in human sebocytes but are also able to enhance them under vitamin A deficient conditions [96, 97].

Vitamin D

Calcitriol, like retinoids, rapidly up-regulates the major vitamin D_3 metabolizing enzyme 24-hydroxylase at the mRNA level, which is an established indicator for calcitriol presence [24]. It enhances the growth-promoting activity of autocrine epidermal growth factor receptor ligands in keratinocytes [98] and can also rapidly increase the activity of 17β-hydroxysteroid dehydrogenase (isotype 2), which leads predominantly in conversion of estradiol to estrone [99]. This estradiol inactivation increases with increased calcitriol levels, especially those who exhibit antiproliferative effects on keratinocytes. In addition, keratinocytes produce abundant PTHrP which is down-regulated by calcitriol suggesting a physiological role [100]. The antiproliferative and anti-inflammatory effects of calcitriol on the skin were shown to be mediated, at least in part, by a complex tumor growth factor-β regulation in dermal fibroblasts [101].

Thyroid Hormones

Hypothyroidism causes disturbances of skin quality and hair character and growth with an increased telogen rate and diffuse alopecia [6, 7]. Replacement reestablishes the normal anagen/telogen ratio. *L*-Triiodothyronine was shown to stimulate proliferation of outer root sheath keratinocytes and dermal papilla cells [102].

PTHrP

Regulation 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 [32].

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 sebocyte differentiation, and PPARδ can ameliorate inflammatory responses in the skin [64]. PPARδ is the predominant subtype in human keratinocytes and is highly expressed in basal and suprabasal cells [103, 104]. Induction of PPARα and PPARγ expression is linked to differentiation, and accordingly, is confined to suprabasal keratinocytes. PPARδ and PPARγ inhibition resulted in a dramatic decrease in proliferation and a robust up-regulation of the expression of involucrin and transglutaminase [104, 105]. Preliminary results have shown expression of PPARδ and PPARγ in the human sebaceous gland [106, 107]. Linoleic acid, a natural PPARδ ligand, induces accumulation of neutral lipids in undifferentiated human sebocytes and reduces spontaneous IL-8 secretion [108]. Estradiol metabolizes prostaglandin D2 to Δ12-prostaglandin J2, a natural ligand for PPARγ [109].

Eicosanoids

Proinflammatory cytokines, such as IL-1β and TNF-α, induce cytosolic phospholipase A_2 expression in keratinocytes and are able to increase the extracellular release of arachidonic acid and stimulate eicosanoid synthesis [31] (fig. 4). Enhanced keratinocyte prostaglandin synthesis after ultraviolet light injury is also due to increased phospholipase activity [30]. The major arachidonic acid metabolites after stimulation with interleukin 1β are prostaglandin E_2 and leukotriene B_4 (LTB_4), while TNF-α stimulates hydroxyeicosatetraenoic acid (HETE) production. IL1α expression has been detected in follicular keratinocytes and sebocytes in vivo and in vitro [73, 110–112]. Interestingly, LTB_4 is a natural ligand for PPARα [113, 114], soluble 15-HETE, which is a natural ligand for PPAR-γ [115], is synthesized in human sebaceous glands [116], and PPARs can regulate lipid and lipoprotein metabolism, cell proliferation, differentiation and apoptosis of various cell types including sebocytes [90]. The axis IL-1/LTB_4/PPARα/lipid synthesis and inflammation was confirmed by a current clinical study; treatment of acne patients with a specific 5-lipoxygenase inhibitor administered systemically led to a 70% reduction in inflammatory acne lesions at 3 months, an approximately 65% reduction in total sebum lipids as well as a substantial decrease in proinflammatory lipids [117].

Release of Skin-Produced 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 organism. Major examples include sex steroids where a large proportion of androgens and estrogens in men and women are synthesized locally in peripheral target tissues from the inactive
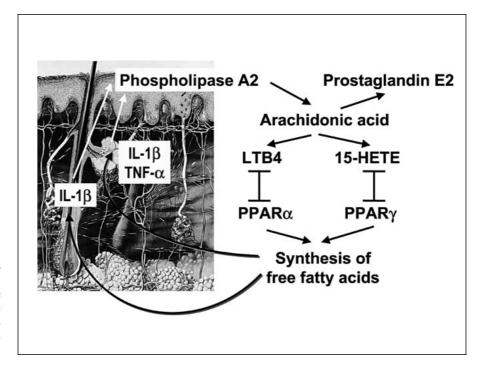
Fig. 4. The cascade of eicosanoid synthesis in the skin. IL-1β = Interleukin-1β; TNF-α = tumor necrosis factor-α; LTB4 = leucotriene B4; 15-HETE = 15-hydroxyeicosatetraenoic acid; PPARα = peroxisome proliferator-activated receptor-α; PPARγ = peroxisome proliferator-activated receptor-γ.

adrenal precursors DHEA and androstenedione. DHEA and androstenedione are converted to testosterone and further to 5α-DHT by the intracellular enzyme 5α-reductase in the periphery, thus making the skin responsible for large amounts of the circulating testosterone and 5α-DHT levels. Up to 50% of the total circulating testosterone is produced in the skin and in other peripheral organs [5]. 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 [82]. Thus, in postmenopausal women, almost all active sex steroids are made in target tissues by an intracrine mechanism.

On the other hand, IGFBP-3 message abundance is greater in the skin that in the liver and circulating IGFBP-3 concentrations are significantly increased by GH and IGF-I [11]. GH has a direct function in the regulation of IGFBP-3 synthesis, and the response of skin IGFBP-3 mRNA levels to both GH and IGF-I suggests that dermal fibroblasts could be more important than the liver in the regulation of circulating reservoir IGFBP-3 in certain circumstances.

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