Skin as an endocrine organ: A narrative review

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Abstract

Skin being the largest organ of the body, is equipped with numerous functional properties. Over the past few years, intricate research into the biology of skin has led to a gamut of discoveries. Skin is now regarded as one of the most vital endocrine organs. The skin contains equivalents of the hypothalamo-pituitary-adrenal axis, hypothalamo-pituitary-thyroid axis and the appendages produce multiple hormones such as Vitamin D, sex steroids, retinoids and opioids. In this article, we will explore the role of skin as a target and source of some of the hormones of the human body, and briefly touch on the clinical applications.

Key words: Endocrine organ, implications, physiology, skin

Introduction

In the past few decades, human skin and its appendages have been identified as endocrine organs themselves, besides being major target tissues for hormones in the body. The scalp hair follicles, for example, have been identified as mini organs which are the target as well as source of multiple hormones, peptides and neurotransmitters participating in the hair cycle.[1] Keratinocytes, sebocytes and adipocytes in skin are now recognised as sources of steroids, peptide hormones and neurotransmitters as well. The skin contains equivalents of the hypothalamo-pituitary-adrenal axis, hypothalamo-pituitary-thyroid axis and the appendages produce multiple hormones such as Vitamin D, sex steroids, retinoids and opioids.[2] In this article, we will take a look at skin as a target and source of these mediators.

Rationale of the Review

The skin serves a multitude of functions in the human body, one of which is its participation in the endocrine system. A few of its endocrine roles are well-known — for instance, production of Vitamin D and effects of retinoids on skin keratinocytes and sebocytes, but many other aspects are yet to be studied in-depth. Limited literature exists on the role of skin as an endocrine organ, however the scope for future research, diagnostic and therapeutic implications remains huge. The skin contains a veritable smorgasbord of receptors ranging from extracellular opioid receptors to intracellular steroid receptors and even intranuclear retinoid receptors; it can also synthesise a vast number of hormones essential to the human body. This review attempting to summarise the existing knowledge of endocrine functions of skin can help further research into these intricate pathways, thus potentially aiding the development of new diagnostic and therapeutic implications for the future. As the most easily accessible organ, skin is uniquely suitable for both the study and management of various conditions in a painless and non-invasive way.

Methods

A comprehensive English literature search was conducted across multiple databases (PubMed, EMBASE, MEDLINE and Cochrane) using the key words (both MeSH and non-MeSH, alone and in combination) 'dermatology' AND/OR 'skin,' 'endocrine functions,' 'hormones,' 'hormone synthesis,' 'hormone targets' and 'receptors.'

Hormone targets in skin and their action

The cells of human skin, especially keratinocytes, sebocytes and follicular keratinocytes, contain receptors for peptides and neurotransmitters on the cell surface, while intracellular receptors are targeted by thyroid and steroid hormones. Some of the cell surface receptors react to substances produced locally, while others have ligands carried in by the blood stream.[2] A summary of hormone receptors in skin is given in Table 1.

Cell surface receptors to locally produced substances

Corticotrophin-releasing hormone receptors

Corticotrophin-releasing hormone receptor 1 is present predominantly in keratinocytes, melanocytes and fibroblasts,

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and corticotrophin-releasing hormone receptor 2 is present in sebocytes.[3,4] They coordinate the stress response by inhibiting keratinocyte proliferation and enhancing immunogenicity through intercellular adhesion molecule-1 molecules, control the cutaneous hypothalamo-pituitary-adrenal axis and stimulate sebaceous lipogenesis.[4-6]

Corticotrophin-releasing hormone released from sensory nerve endings and immunoregulatory cells in skin can trigger the cutaneous equivalent of the hypothalamo-pituitary-adrenal axis, in response to stress on skin. This may help to limit skin damage. Corticotrophin-releasing hormone receptor 1 agonists and antagonists can be a potential therapeutic agent for skin diseases worsening with stress such as psoriasis and atopic dermatitis.[5] Corticotrophin-releasing hormone receptor 2 in sebocytes can be implicated in skin disorders with sebaceous origin like acne.[4]

Thyroid-stimulating hormone receptors

Thyroid-stimulating hormone receptors are detected in keratinocytes, both epidermal and follicular, melanocytes and dermal fibroblasts.[7] They stimulate biological activity of keratinocytes and modulate keratin expression.[2] These thyroid-stimulating hormone receptors may be acted on by autoantibodies against thyroid-specific antigens to produce cutaneous changes in autoimmune thyroid disorders.[8]

Parathyroid hormone/parathyroid hormone-related peptide receptors

They are present in dermal fibroblasts.[9] They regulate fibroblast proliferation, keratinocyte proliferation and maturation, skin angiogenesis and hair growth.[9-12] They help maintain normal dermal physiology. Parathyroid hormone/parathyroid hormone-related peptide receptor agonists and antagonists may be explored as potential therapy for chemotherapy-induced alopecia.[10]

Melanocortin receptors

Melanocortin 1 receptor have high affinity for alpha-melanocyte-stimulating hormone and adrenocorticotrophic hormone and are located in keratinocytes, melanocytes, endothelial cells, dermal fibroblasts and sebocytes. Melanocortin 2 receptors bind to adrenocorticotrophic hormone and are located in adipocytes. Melanocortin 5 receptor binds to alpha-melanocyte-stimulating hormone and adrenocorticotrophic hormone; it is located in sebocytes and sweat gland cells.[13,14]

Alpha-melanocyte-stimulating hormone and adrenocorticotrophic hormone play a role in the pigmentation of skin and tanning response; these are enhanced by ultraviolet light and enacted through cyclic adenosine monophosphate

Table 1: Hormone receptors present in skin

Location of receptor	Name of receptor	Salient features
Cell surface receptors (to locally produced substances)	Corticotrophin-releasing hormone receptor	Coordinate stress response and initiate hypothalamo-pituitary-adrenal axis equivalent in skin
	Thyroid-stimulating hormone receptor	Stimulates biological activity of keratinocyte
	Parathyroid hormone/parathyroid hormone-related peptide receptor	Regulate fibroblast, keratinocyte and angiogenesis
	Melanocortin receptor	Regulates skin pigmentation and immunomodulatory effects
	μ-opiate receptor	Mediates itch, skin pigmentation and stress-induced acne
	Melatonin receptor	Antioxidant role to prevent carcinogenesis
	Serotonin receptor	Participates in allergic reactions and pruritus
	Vasoactive intestinal polypeptide receptors	Histamine release and vasodilation
	Endocannabinoid receptor	Inhibits inflammation
	Insulin/insulin-like growth factor I, epidermal growth factor and growth hormone receptors	Maintain cutaneous homeostasis by regulating cell proliferation and differentiation
	Prolactin receptors	Possible role in sebum production, keratinocyte proliferation and thermoregulation
Cell surface receptors (to substances generated outside skin)	Calcitonin gene-related peptide receptors and proteinase-activated receptors	Anti-inflammatory, also modulate keratinocyte growth and proliferation
	Substance *P* acting on neurokinin 1 receptor	Mast cell degranulation
	Dopamine receptor	Inhibits hair growth (not very significant)
Intracellular receptors	Glucocorticoid receptor	Multiple roles such as regulating keratinocyte differentiation, ageing, hair follicle growth and local immunomodulation
	Androgen receptor	Influences hair growth, responsible for patterned baldness
	Progesterone receptor	Role not clear
Intranuclear receptors	Thyroid hormone receptor	Regulates keratinocyte and hair follicle proliferation and differentiation
	Oestrogen receptor (oestrogen a and oestrogen b)	Anti-inflammatory and anti-apoptotic role in skin
	Retinoic acid receptors (α γ) and retinoid X receptor (α, β, γ)	Maintain skin homeostasis, integrity of skin barrier and inhibit lipid synthesis
	Vitamin D receptor	Help regulating epidermal proliferation and differentiation
	Peroxisome proliferator-activated receptors (α, γ, δ)	Most well-known role of peroxisome proliferator-activated receptors γ is in lipid biosynthesis

Table 2: Hormones synthesised/metabolised in the skin

Hormones synthesised/metabolised	Tissue of synthesis/metabolism
• Parathyroid hormone-related peptide	Keratinocytes (also present in but not synthesised in melanocytes)
• Corticotrophin-releasing hormone • Urocortin	Sebocytes, follicular keratinocytes, endothelial cells, dermal nerves Epidermal and follicular keratinocytes, sweat glands, epidermal melanocytes, dermal smooth muscle cells and fibroblasts, endothelial cells
Pro-opiomelanocortin peptides: • Adrenocorticotrophic hormone, Alpha-melanocyte-stimulating hormone • β-Endorphin	Epidermal keratinocytes, melanocytes, outer root sheath of anagen follicles, dermal fibroblasts, endothelial cells Outer root sheath of anagen follicles, dermal fibroblasts
• PRL	Dermal fibroblasts
• Catecholamines (epinephrine and norepinephrine)	Keratinocytes
• Insulin-like growth factor-I	Dermal fibroblasts (also produce insulin-like growth factor II, insulin-like growth factor binding protein-3), melanocytes, keratinocytes of stratum granulosum
• Sex steroids (androgens, oestrogen, progesterone) • Prednisolone	Sebaceous and sweat glands with intracellular activation depending on expression of enzymes Keratinocytes
• Retinoids (all-transretinoic acid)	Low amounts in keratinocytes
• Vitamin D	Keratinocytes
• Eicosanoids (prostaglandins, prostacyclins and leukotriene)	Keratinocytes, sebocytes

and tyrosinase-dependent pathways.[3,14] Alpha-melanocyte-stimulating hormone directs production of eumelanin, increases melanocyte dendricity and their attachment to extracellular matrix proteins and protects melanocytes from oxidative stress.[15] Alpha-melanocyte-stimulating hormone also has immunomodulatory effects; it downregulates pro-inflammatory cytokines such as interleukin-1, interleukin-6 and tumour necrosis factor alpha and upregulates anti-inflammatory cytokines like interleukin-10 in keratinocytes.[14,16] Similarly, it can modulate activation of nuclear factor kappa b and activator protein-1, secretion of interleukin-8, induction of collagenase in dermal fibroblasts, hence regulating extracellular matrix formation, wound healing, angiogenesis, etc.[17] Alpha-melanocyte-stimulating hormone can modulate allergic responses by controlling histamine release from mast cells and activation of basophils.[18,19] It can have a protective action on hair follicles by prolonging anagen and helping in retaining immune privilege.[2,3,10] Due to its multiple roles, alpha-melanocyte-stimulating hormone is being investigated in numerous skin disorders as potential therapy; for example, as an anti-inflammatory agent in psoriasis.[20]

μ-opiate receptors

They bind tightly to β-endorphins and have been detected in keratinocytes of the epidermis and hair follicles, sebocytes, melanocytes and secretory part of sweat glands.[3,21] They release histamine from mast cells and mediate itch, regulate skin pigmentation by melanogenic and dendritogenic effects and increase lipogenesis in sebocytes.[18,21,22] They may have a role in stress-induced acne.[22]

As seen above, pro-opiomelanocortin derivatives have a broad list of functions in the skin.

Melatonin receptors

Type 1 (Melatonin 1) receptors are present in epidermal and follicular keratinocytes and melanocytes as well as fibroblasts, while type 2 (Melatonin 2) is only seen in neonatal keratinocytes. Melatonin can cause hair growth, but its major function is as an antioxidant that can prevent skin carcinogenesis.[23]

Serotonin receptors

Serotonin R1A, serotonin R1B and serotonin R2A receptors can be detected in epidermal keratinocytes, melanocytes and dermal fibroblasts. Serotonin R2C is found in hair follicle melanocytes and fibroblasts while serotonin 2B and serotonin 7 are seen in normal skin.[24] They have variable effects on the growth of cells, especially melanocytes, and primarily participate in allergic reactions and pruritus related to some skin diseases such as cholestatic or uremic pruritus and urticaria.[23] They have a proven role in inciting allergic contact dermatitis.[25] The cutaneous serotonergic/melatoninergic system is active continuously, in contrast to the pineal gland which is governed by the circadian rhythm. This system maintains skin homeostasis in response to external and internal stress.[23]

Vasoactive intestinal polypeptide receptors

These are present in sweat glands, mast cells, keratinocytes of basal layer, endothelial cells, mononuclear cells and nerve fibres in the dermis. Vasoactive intestinal polypeptide can induce histamine release, cause vasodilation and participate in regulation of sweat and allergic responses in the skin.[26-28]

Vasoactive intestinal polypeptide receptor upregulation by cytokines can incite inflammation in skin diseases such as atopic dermatitis and psoriasis.[29]

Endocannabinoid receptors

Locally produced cannabinoids like anandamide act on CB1 and CB2 receptors to regulate cell growth, inhibit inflammation, inhibit hair growth and promote lipogenesis in sebocytes.[30] They have a protective role in allergic contact dermatitis and other inflammatory skin diseases by suppressing inflammation, and agonists may be used potentially in skin tumours, psoriasis, hirsutism, dryness and dermatitis. CB2 agonists can decrease dermal fibrosis and have a potential therapeutic role in systemic sclerosis. CB antagonists may have a role in alopecia areata and acne.[30]

Insulin/insulin-like growth factor I, epidermal growth factor and growth hormone receptors

Insulin-like growth factor-I and epidermal growth factor receptors are present in proliferating epidermal keratinocytes with insulin-like growth factor-I receptors also being detected in melanocytes and fibroblasts.[31,32] Growth

hormone receptors are located in epidermal and follicular keratinocytes, melanocytes, fibroblasts, sweat and sebaceous glands, endothelial cells, matrix of dermal papillae, etc.[32-34]

These act to maintain homeostasis in the cutaneous environment by regulating cell proliferation and differentiation. Growth hormone has limited direct impact on skin cells and the majority of its effects are mediated indirectly by insulin-like growth factors.[13] Growth hormone and insulin-like growth factor both induce sebocyte differentiation and promote lipid synthesis in sebocytes, but insulin-like growth factor and insulin can also promote sebocyte proliferation.[35] Growth hormone does not stimulate proliferation of sebocytes or keratinocytes, but it can promote fibroblast proliferation.[32,35] Insulin-like growth factor-1 can modulate hair follicle proliferation and differentiation and plays an important role in hair growth cycle.[36] Insulin-like growth factor-1 also promotes keratinocyte proliferation and inhibits keratinocyte differentiation.[37,38] The growth hormone/insulin-like growth factor-1 axis may have interactions with the cutaneous hypothalamo-pituitary-adrenal axis equivalent.[13]

Insulin-like growth factor-1 is useful for maintaining human skin in organ culture.[31]

Prolactin receptors

These are present in keratinocytes, fibroblasts, sweat glands and pilosebaceous units. They have been shown to promote sebum production and are postulated to have a role in keratinocyte and sebocyte proliferation and differentiation. They may also have a role in thermoregulation.[39] Prolactin may contribute to psoriasis by stimulating keratinocyte proliferation and angiogenesis and to cutaneous autoimmune diseases such as lupus and Behcet's syndrome by promoting immune cells like B lymphocytes, Th1 lymphocytes and dendritic cells. Antagonists like bromocriptine may have a potential role in controlling such disorders.[39]

Cell surface receptors reacting to substances generated outside skin

Calcitonin gene-related peptide receptors and proteinase-activated receptors

Calcitonin gene-related peptide receptors are expressed on cutaneous Langerhans cells while calcitonin gene-related peptide is released from epidermal nerve endings; it suppresses immune reactions and has an anti-inflammatory action.[40] Calcitonin gene-related peptide can also help retain immune privilege of hair follicles.[41] Proteinase-activated receptors are present on keratinocytes; they can modulate growth and differentiation. Proteinase-activated receptor 2 is found on endothelial cells and neutrophils and mediates their interaction. Proteinase-activated receptor 2 agonists have been found to help release neuropeptides including calcitonin gene-related peptide causing vasodilation, itching and pain.[42]

Substance P acting on neurokinin 1 receptor

Substance P is a stress hormone released from nerve endings. It causes mast cell degranulation and causes hair follicles to go into premature catagen.[43] It can also promote sebaceous gland proliferation and differentiation.[44]

Dopamine receptors

Dopamine 1 receptor has been shown to inhibit hair growth in human hair follicle.[2,45]

Intracellular receptors

They are located either in the nucleus or in the cytoplasm, but their action is in the nucleus. They associate to the 'hormone response element,' a specific region in the nuclear DNA and regulate the transcription of different molecules to exert their biological effects.[13]

The steroid receptors reside in the cytoplasm as polymeric complexes and are transported to the nucleus for action. They include the following:

Glucocorticoid receptor

This is expressed in the cytoplasm of keratinocytes, mainly in the basal layer, Langerhans cells and fibroblasts.[46] Glucocorticoids inhibit early differentiation of keratinocytes, but promote terminal epidermal differentiation; they inhibit keratinocyte proliferation and contribute to skin atrophy.[47] They inhibit wound healing by prohibiting keratinocyte migration.[48] They contribute to skin ageing, enhance lipid synthesis and upregulate hair follicle growth.[49] Human sebocytes contain glucocorticoid receptors and are increased in number by glucocorticoid activity – as witnessed in acne lesions.[50] The hypothalamo-pituitary-adrenal axis has a mini counterpart in the hair follicles which are responsive to steroids.[50]

Topical steroids, as we know, are used in a wide variety of dermatoses like eczema including atopic dermatitis, vitiligo, mild-to-moderate psoriasis, lichen planus, mycosis fungoides, bullous pemphigoid, cutaneous sarcoid and alopecia areata.[51] Intralesional injections can be used for alopecia areata, keloids, prurigo nodularis, cystic acne, etc., while systemic steroids may be used for bullous dermatoses, connective tissue diseases such as systemic lupus erythematosus and dermatomyositis, severe dermatitis, urticaria and neutrophilic dermatoses.[52]

Androgen receptor

The androgen receptor has been localised to keratinocytes, fibroblasts, endothelial cells, eccrine sweat glands, external root sheath of hair follicles, dermal papilla, sebocytes and genital melanocytes.[53,54] Androgens can be synthesised in skin, and weaker androgens can be converted to stronger ones locally; for example, dehydroepiandrosterone (weak) to testosterone (potent) to dihydrotestosterone (most potent and main hormone). The second step is catabolised by 5-alpha reductase.[55] Androgens stimulate sebocytes and increase sebaceous gland activity, more on the face than in non-facial areas.[56] They act on dermal papilla cells and influence hair growth with different effects in different sites – baldness on the scalp but growth in the beard with no effect on eyelashes.[57] They also have effects on epidermal barrier homeostasis, skin ageing and wound healing.[58]

Androgen-dependent dermatoses include acne vulgaris, androgenetic alopecia and hirsutism.[55] Oral contraceptives containing oestrogen and progesterone suppress androgens and are effective in females with the above disorders especially if they are associated with polycystic ovary syndrome. Anti-androgens cyproterone acetate and spironolactone also have

similar roles. Finasteride, a 5-alpha reductase inhibitor, is useful in males with androgenetic alopecia.[58]

Progesterone receptor

This has been located in keratinocytes and melanocytes.[59,60] It has an inconsistent action on melanocytes.[60] As mentioned above, progesterone and its analogues are used in combination pills in androgen-related disorders.

The thyroid group of receptors resides mainly in the nucleus; they exert their actions locally. These include:

Thyroid hormone receptors (TRa and TRb)

They are located in keratinocytes, pilosebaceous units (dermal papilla, outer root sheath and sebocytes) and fibroblasts.[61-63] In hyperthyroid patients, skin is hot, sweaty and itchy while in hypothyroid skin is dry, cold and rough. This demonstrates how thyroid hormone regulates keratinocyte proliferation and differentiation.[64] These receptors also ensure normal hair follicle growth.[65]

Oestrogen receptors (α, β)

They are found in keratinocytes and fibroblasts mainly, but also in hair follicles (dermal papilla, outer root sheath), adipocytes and melanocytes.[66-68] Oestrogen increases skin thickness and collagen content, retains moisture and delays skin ageing and wrinkles.[66] Oestrogen increases number of melanocytes but decreases their melanin content and tyrosinase acitivity.[68] Oestrogen stimulates keratinocyte proliferation and acts as an anti-inflammatory and anti-apoptotic factor; it stimulates hair growth by prolonging the growing phase (as during pregnancy).[69]

As seen above, oestrogen and progesterone combined pills have a role in androgen-related diseases in females. However, oestrogen containing pills or creams can cause pigmentation as a side effect.[58]

Retinoic acid receptors α, γ and retinoid X receptor α, β, γ

These are expressed in various skin cells such as keratinocytes, melanocytes, fibroblasts and sebocytes; retinoid X receptors are also seen in inflammatory cells like Langerhans cells.[70-73] Retinoic acid receptor γ and retinoid X receptors cause increased epidermal proliferation and increased target gene expression while retinoic acid receptor α prevents these effects; thus, they act to maintain homeostasis of skin and dysregulation may lead to a defective skin barrier.[74] Retinoids inhibit proliferation and lipid synthesis in sebaceous glands (mechanism of treatment in acne).[75]

Retinoids, topical and systemic, maintain a balance between epidermal proliferation and desquamation; hence, they are useful in hyperkeratotic and parakeratotic disorders like psoriasis, keratotic genodermatoses such as ichthyosis, severe acne and acne-related diseases and treatment as well as prevention of skin cancer.[76]

Vitamin D receptors

Vitamin D can be produced in the skin keratinocytes and converted to its active form 1,25-dihydroxyvitamin D. Vitamin D receptors are present in keratinocytes of the epidermis and hair follicles.[77] They are also detected in other skin appendages, melanocytes and in immune cells like Langerhans cells, certain macrophages and lymphocytes.[78] Vitamin D receptors can regulate epidermal proliferation and differentiation (increase or decrease as per requirement), help in normal hair growth cycle and also act as tumour suppressors.[77]

Vitamin D deficiency has been detected in psoriatic patients and topical Vitamin D is useful in psoriasis. Topical vitamin D is also useful in treating vitiligo though the role of deficiency is not clear. Low Vitamin D levels could cause hair loss and exacerbate atopic dermatitis and supplements can improve these conditions.[79]

Peroxisome proliferator-activated receptors (PPARs α/γ/δ)

These are present in keratinocytes and sebocytes and some adipocytes.[80] Peroxisome proliferator-activated receptor α helps in maintaining skin barrier, peroxisome proliferator-activated receptor γ helps in lipid biosynthesis in keratinocytes and sebocytes and facilitates differentiation of the cells, while peroxisome proliferator-activated receptor δ can reduce inflammatory responses.[80,81]

Hormone synthesis in skin

Multiple hormones are synthesised in skin. The major ones are given below. Figure 1 summarises the hormones produced in skin. The hormones have been summarised in Table 2.

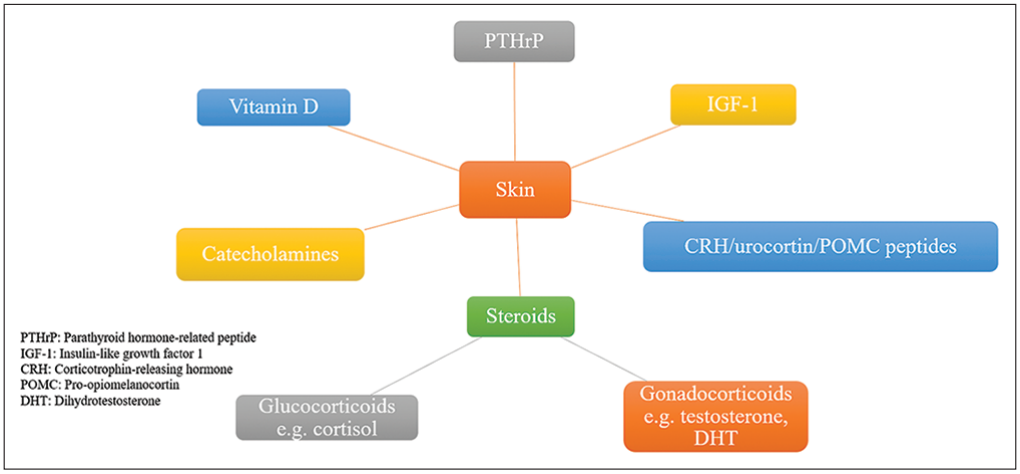

Figure 1: Hormones produced in the skin

Parathyroid hormone-related peptide

It is produced by epidermal and follicular keratinocytes and may have a role in hair growth and differentiation of epidermal cells in either autocrine or paracrine fashion.[82] It may also be produced in melanocytes.[83]

Steroids

The cutaneous system has the full machinery to produce corticosteroids and sex steroids, either from systemically derived precursors or through local conversion of cholesterol to pregnenolone to progesterone and so on. Production of corticosterone and cortisol has been detected not only in keratinocytes but also in epidermal melanocytes and dermal fibroblasts.[84] The pilosebaceous unit can synthesise sex steroids and convert weaker androgens to more potent forms and have been shown to contain the enzymes steroid sulfatase, 3β-hydroxysteroid dehydrogenase, 17β-hydroxysteroid dehydrogenase, 5α-reductase, 3α-hydroxysteroid dehydrogenase and aromatase.[55] Dehydroepiandrosterone may be formed from dehydroepiandrosterone-S of adrenal glands or synthesised *de novo* in skin which can further be metabolised to androstenedione to testosterone. Testosterone to dihydrotestosterone conversion is limited as low levels of dihydrotestosterone are required for skin homeostasis.[84]

Corticotrophin-releasing hormone, urocortin and pro-opiomelanocortin peptides

The skin is believed to contain a corticotrophin-releasing hormone/pro-opiomelanocortin axis analogous to hypothalamo-pituitary-adrenal axis in the body for dealing with stress. Corticotrophin-releasing hormone is produced in response to stress in keratinocytes, melanocytes, endothelial cells and dermal nerves.[4] This corticotrophin-releasing hormone acts on nearby corticotrophin-releasing hormone receptors; corticotrophin-releasing hormone increases production and secretion of pro-opiomelanocortin peptides.[3,13] Pro-opiomelanocortin peptides include adrenocorticotrophic hormone, alpha-melanocyte-stimulating hormone and β-endorphin which all have a role in regulating immune responses in the skin. Adrenocorticotrophic hormone and alpha-melanocyte-stimulating hormone are expressed in keratinocytes, melanocytes, endothelial cells, outer root sheath of hair follicles and fibroblasts; β-endorphin is found in the last two.[3,14] The production of corticotrophin-releasing hormone and pro-opiomelanocortin peptides is stimulated by ultraviolet rays which are a stress factor for the skin.[3] Urocortin is a corticotrophin-releasing hormone-related peptide acting on corticotrophin-releasing hormone receptor and expressed in keratinocytes, sweat glands, melanocytes, blood vessel wall, dermal smooth muscle, fibroblasts and some inflammatory cells.[85]

Vitamin D

Skin is a unique site where Vitamin D3 is produced. It is converted by the liver to 25-hydroxyvitamin D3; 25-hydroxyvitamin D3 is further converted to 1,25-dihydroxyvitamin D3 (calcitriol) in keratinocytes. They can also deactivate calcitriol by 24-hydroxylation.[86] Dermal fibroblasts are shown to contain inactive Vitamin D3 metabolites which may be activated by keratinocytes on stimulation with ultraviolet rays.[87]

Prolactin may have an intracutaneous source, but evidence is still insufficient.[39]

Catecholamines

Epinephrine and nor-epinephrine act through the cyclic adenosine monophosphate pathway; they were known to be synthesised in keratinocytes but have recently been detected in melanocytes as well. They have autocrine effects on regulation of sweating and cutaneous blood supply, along with some effects on wound healing and melanocytes.[2,88]

Insulin-like growth factor 1

Insulin-like growth factor 1 is synthesised in dermal fibroblasts, stratum granulosum keratinocytes and melanocytes.[89,90] Insulin-like growth factor 2 is produced in dermal fibroblasts.[91]

Conclusion

Not only is the skin acted on by multiple hormones, it is also a factory for the synthesis of many chemicals which usually have autocrine or paracrine functions. Apart from this, the skin is also a window into the abnormalities of the endocrine system, as many endocrine disorders primarily present with skin manifestations.

The endocrine function of the skin, in spite of multiple possible therapeutic and diagnostic implications, is not yet very comprehensively researched. Melanocortin receptors for example, also control skin immune responses, matrix formation, wound healing, hair follicle metabolism, etc., besides regulating pigmentation which was thought to be their principal function.[10,16,17] Serotonin receptors in skin help maintain homeostasis. The role of androgen and oestrogen/progesterone receptors in skin is yet to be fully elucidated. New studies are coming up daily regarding using the cutaneous endocrine system to regulate not only skin diseases but also systemic conditions. The possible role of the corticotrophin-releasing hormone system in acne vulgaris, the scope of topical parathyroid hormone/parathyroid hormone-related peptide agonists in chemotherapy-induced alopecia and psoriasis and that of topical cannabinoids in acne for their antimicrobial action are upcoming research topics. Alpha-melanocyte-stimulating hormone agonists are being studied for their efficacy in psoriasis, porphyrias and sarcoidosis.[92-94] Transdermal delivery of Vitamin D, the effect of topical Vitamin D in preventing skin ageing and potential use of topical Vitamin D in eye diseases are being investigated.[95-97] Further research is needed to more completely unravel the role the cutaneous system plays with regard to the synthesis, action and metabolism of hormones.

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Conflicts of interest

There are no conflicts of interest.

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