The role of hypothalamus-pituitary-adrenal (HPA)-like axis in inflammatory pilosebaceous disorders

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Abstract

Skin is the largest peripheral endocrine organ and functions as a hormone target and endocrine gland. A cutaneous hypothalamus-pituitary-adrenal (HPA)-like axis enables the skin to respond to stress and regulates its steroidogenic activity. The pilosebaceous unit is a site for production and metabolism of a number of steroid hormones, including stress and sex hormones. This is an overview of the important role that the cutaneous HPA-like-axis plays in the pathogenesis and treatment of inflammatory pilosebaceous disorders, including acne, rosacea, seborrheic dermatitis, and hidradenitis suppurativa.

Keywords: steroidogenesis, acne, seborrheic dermatitis, hidradenitis suppurativa, HPA, stress

Abbreviations

ACTH	adrenocorticotropic hormone
C. albicans	*Candida albicans*
CRH	corticotropin releasing hormone
DHEAS	dehydroepiandrosterone sulfate
DHT	dihydrotestosterone
ER	endoplasmic reticulum
FFA	free fatty acids
FGFRs	fibroblast growth factor receptors
GRH	gonadotropin releasing hormone
HPA	hypothalamus-pituitary-adrenal
HS	hidradenitis suppurativa
IGF	insulin-like growth factor
IL	interleukin
MC5R	melanocortin-5-receptors
MSH	melanocyte stimulating hormone
mTORC1	mechanistic target of rapamycin complex 1
NRS	National Rosacea Society
OCPs	oral contraceptive pills
P. acnes	*Propionibacterium acnes*
PGA	physician global assessment
POMC	proopiomelanocortin
PPARs	peroxisome proliferator-activated receptors
PSU	pilosebaceous unit
SD	seborrheic dermatitis
SG	sebaceous gland
SHBG	sex hormone binding globulin
TEWL	transepidermal water loss
TLR2	toll-like receptor 2
TNF	tumor necrosis factor
TRH	thyrotropin releasing hormone
UV	ultraviolet
VEGF	vascular endothelial growth factor

Introduction

Pilosebaceous Unit (PSU)

The pilosebaceous unit (PSU) consists of a sebaceous gland (SG) and an associated hair follicle (**Figure 1**), [1]. Sebaceous glands secrete sebum, which coats the hairs and is released along the hair shaft onto the skin surface [2]. Most of the sebaceous lipids are synthesized *de novo* and consist of squalene, cholesterol, cholesterol esters, wax esters, and triglycerides [2]. Sebum functions as a hydrophobic coating to reduce transepidermal water loss (TEWL) and maintain skin moisture and smoothness [2].

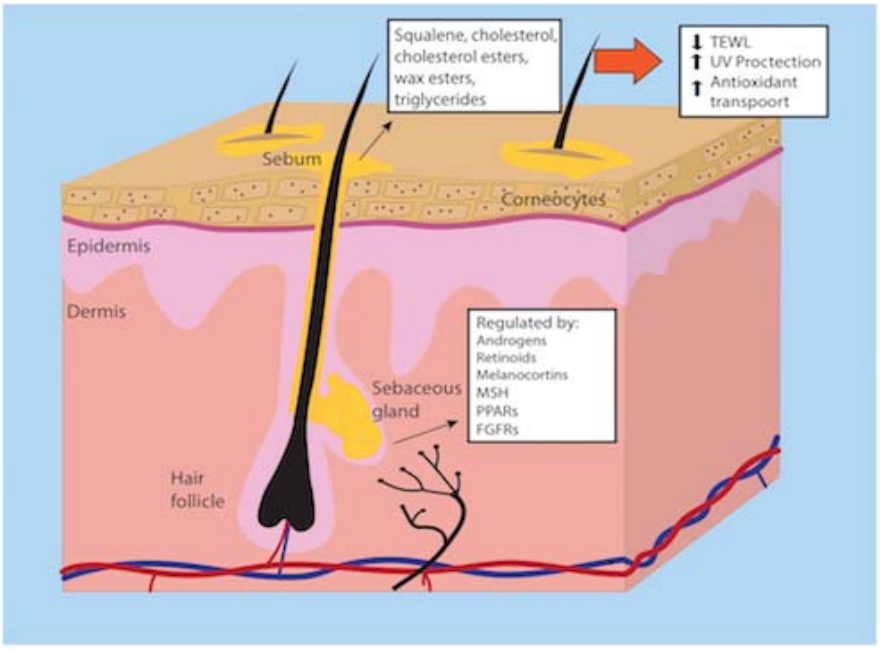

Figure 1. *Normal pilosebaceous unit. The pilosebaceous unit consists of sebaceous gland and an associated hair follicle. The sebaceous gland function is regulated by androgens, retinoids, melanocortins, MSH, PPARs, and FGFRs. The sebaceous glands secrete an oily substance called sebum, which coats the hair and is released along the hair shaft onto the skin's surface. The sebaceous lipids consist of squalene, cholesterol, cholesterol esters, wax esters, and triglycerides. These lipids provide hydrophobic coating and as a result help reduce trans epidermal water loss, increase ultraviolet protection, aid in antioxidant transport to and from skin's surface, as well as maintain skin moisture and smoothness.*

Sebum also aids in transport of fat-soluble antioxidants to and from the skin surface [3] and protects the skin from ultraviolet (UV) irradiation [4]. Sebum production is regulated by both neural and endocrine controls. *In vitro* and animal studies suggest that SGs are regulated by androgen hormones, retinoids, melanocortins [adrenocorticotropic hormone (ACTH) and melanocyte stimulating hormone (MSH)], peroxisome proliferator-activated receptors (PPARs), and fibroblast growth factor receptors (FGFRs), [5].

Androgens and PSU

Sebaceous glands express all enzymes necessary for de-novo steroidogenesis, as well as conversion of weaker androgens into more potent ones (**Figure 2**), [1, 6]. Dehydroepiandrosterone sulfate (DHEAS), a weak androgen, is converted to more potent androgens (testosterone and dihydrotestosterone (DHT)) within the SG [1]. Androgen receptors within the PSU respond to both testosterone and its more potent counterpart, DHT [7]. End organ receptor sensitivity within the PSU plays a major role in the function of androgens. Individuals with complete androgen insensitivity lack detectable sebum secretion and as a result, do not develop acne vulgaris [8]. Starting at age twenty, sebum secretion begins to decline by 23% per decade in men and 32% per decade in women [9], which parallels the decline in serum DHEAS levels [10].

Hepatic synthesis of insulin-like growth factor (IGF)-1 in response to growth hormone release by the pituitary gland has a direct impact on SG function [11]. IGF-1 exerts its effects on the PSU via the IGF-1/AKT/mTORC1/SREBP1 signaling pathway, which is responsible for androgen production and sebogenesis [12]. Insulin-like growth factor-1 regulates androgen synthesis, androgen metabolism, and end organ androgen sensitivity [13]. Specifically, IGF-1 induces adrenal and gonadal androgen synthesis, promotes the expression of 5-α-reductase, and thus increases conversion of testosterone to DHT [13, 14]. Insulin-like growth factor-1 also depletes FoxO1, an important negative regulator of androgen receptor transactivation, via AKT-mediated phosphorylation [13]. Furthermore, basal and suprabasal sebocytes express IGF-1 receptor [15]. Insulin-like growth factor-1 [16] and androgens [17] both increase sebocyte SREBP1c expression, a key transcription factor in sebaceous lipogenesis. Insulin and IGF-1 activate the mechanistic target of rapamycin complex 1 (mTORC1), which stimulates expression of peroxisome proliferator-activated receptor-γ and SREBP1c, leading to increased sebogenesis [12, 13].

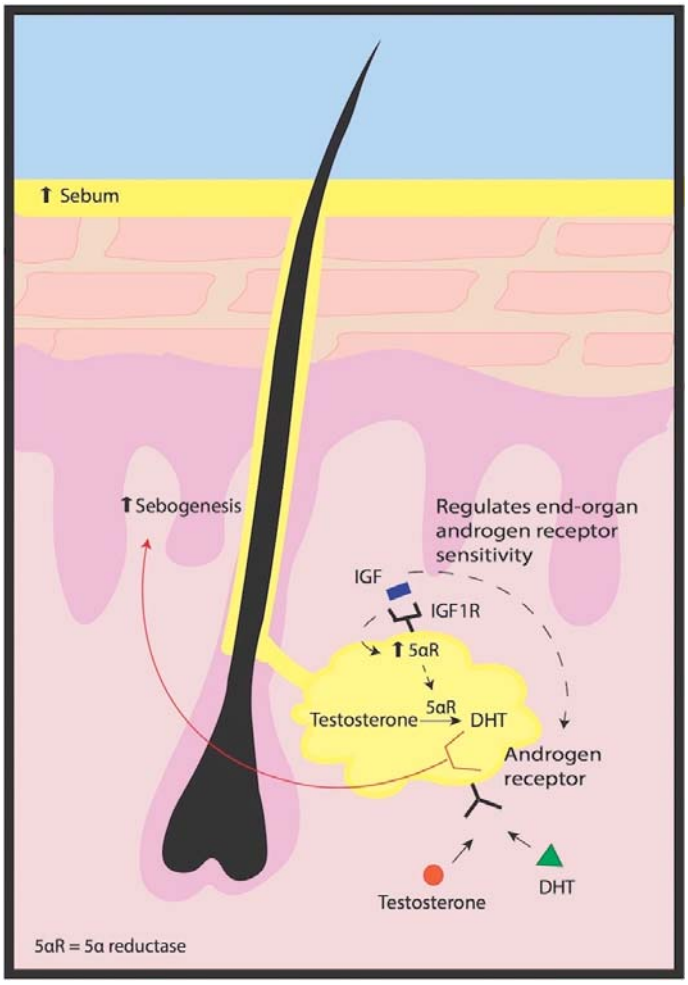

Figure 2 *Androgens and the pilosebaceous unit. Sebaceous glands not only contain enzymes needed for de-novo steroidogenesis, but also enzymes needed for the conversion of weaker androgens into more potent ones. Growth hormone (not pictured) is released by the pituitary gland and stimulates IGF-1 synthesis in the liver. Subsequently, IGF-1 induces adrenal and gonadal production of androgens. In the skin, IGF-1 exerts its effects on the sebaceous unit via the IGF-1/AKT/mTORC1/SREBP1 signaling pathway, which affects androgen and sebum production, androgen metabolism, and end organ androgen sensitivity. Specifically, IGF-1 promotes the expression of enzyme 5-α-reductase, increasing the conversion of testosterone to DHT. Additionally, it increases sebogenesis and end-organ androgen receptor sensitivity. IGF1R, insulin-like growth factor-1 receptor; 5αR, 5-α-reductase.*

Systemic and cutaneous stress response systems

Systemic stress leads to hypothalamic release of corticotropin releasing hormone (CRH), which activates CRH receptors in the pituitary gland, leading to synthesis and release of proopiomelanocortin (POMC)-derived peptides (MSH and ACTH), (**Figure 3A)**, [18]. Adrenocorticotropic hormone enters the peripheral

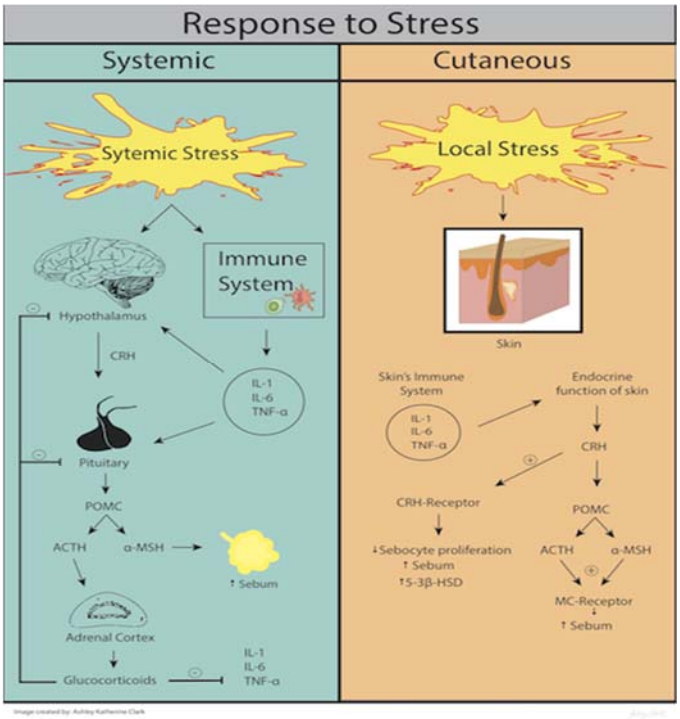

Figure 3. *Systemic stress response system (left) compared to cutaneous stress response (right).*

Systemic stress response system (left) In response to systemic stress, hypothalamus releases CRH, which subsequently activates CRH receptors in the pituitary gland, leading to synthesis and release of POMC-derived peptides, ACTH and MSH, by the pituitary gland. Subsequently, ACTH enters peripheral circulation and stimulates rapid synthesis and release of glucocorticoid hormones, including cortisol (stress response hormone), by the adrenal glands. MSH stimulates sebum synthesis by the sebaceous glands. The secretion of cortisol is controlled via negative feedback mechanisms, in which plasma cortisol inhibits CRH release by the hypothalamus and ACTH release by the pituitary, as demonstrated in this figure. (For other negative feedback mechanisms, see text). In response to systemic stress, the immune system generates pro-inflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor (TNF), which also stimulate the HPA-axis to increase cortisol production. When cortisol is produced, it exerts its anti-inflammatory properties by inhibiting IL-1, IL-6, and TNFα.

Cutaneous stress response (right) In response to external stressors, including pro-inflammatory cytokines IL-1, IL-6, and TNF, the skin stress response system involves only locally produced CRH and POMC. The locally produced CRH stimulates the CRH receptors, resulting in inhibition of sebocyte proliferation, increased sebum production, and enhanced expression of Δ5-3β-hydroxysteroid dehydrogenase, an enzyme responsible for androgen activation. Furthermore, CRH leads to local production of POMC-derived peptides, ACTH and MSH, which stimulate the MC receptors to increase sebum production. 5-3β-HSD, Δ5-3β-hydroxysteroid dehydrogenase; IL-1, interleukin-1; IL-6, interleukin-6; MC-Receptor, melanocortin receptor; POMC, propiomelanocortin; MSH, α-melanocyte stimulating hormone.

circulation to stimulate adrenal DHEAS and cortisol production [19]. In addition, cortisol is produced by the hair follicles [20]. Cortisol is a stress response hormone [21] and has versatile anti-inflammatory properties [18]. Its secretion is controlled via three major negative feedback mechanisms: 1) by plasma cortisol [22], which inhibits CRH and ACTH secretion in hypothalamus and pituitary, 2) by pulsatile secretion of ACTH [23], which is dependent on circadian rhythm and peaks around 6-8am on a typical sleep cycle, and 3) by emotional and physical stress [24], which stimulate CRH secretion from sites other than hypothalamus, including the skin. Cortisol in turn terminates the stress response and attenuates CRH and POMC peptide production, closing the negative feedback loop [18]. Pro-inflammatory cytokines, such as IL-1, IL-6, and tumor necrosis factor (TNF) stimulate the HPA-axis [18] leading to cortisol increase.

The SG is analogous to the "brain of the skin" [25] and provides the peripheral equivalent of the HPA-axis [26]. The skin responds to and synthesizes stress mediators such as CRH, ACTH, cortisol, and catecholamines [26]. In contrast to the systemic stress response system, the skin stress response involves only locally produced CRH and POMC synthesized in response to external stressors, including proinflammatory cytokines [18, 26]. Corticotropin releasing hormoneis the most proximal hormone in the cutaneous HPA-like axis, whereas the CRH-binding protein and corticotrophin receptors act as downstream regulators (**Figure 3B**). Corticotropin releasing hormone inhibits sebocyte proliferation, induces production of sebaceous lipids, and enhances expression of Δ5-3β-hydroxysteroid dehydrogenase, an enzyme responsible for androgen activation [25, 27]. Thus, CRH-stimulation may play a role in the development of acne, rosacea, and other skin disorders associated with alterations in lipid synthesis by SG [25, 27].

Melanocortins (ACTH and α-MSH) stimulate sebaceous squalene production by sebocytes derived from normal facial skin [28]. Melanocortin-5-receptors (MC5-R) are found in SG, and regulate sebaceous function [29]. Rodent studies have confirmed that melanocortins increase sebum production and that targeted disruption of MC5-R leads to decreased sebum production [30]. During stress, ACTH acts on SG to mediate steroidogenesis and sebum production [29]. Melanocortins mediate SG hormonal responses to stress and present a link between stress and acne exacerbation [29]. The cutaneous HPA-like axis involves the intricate interaction between the PSU and its associated steroid hormones and plays an important role in the pathogeneses and treatment of acne vulgaris, rosacea, seborrheic dermatitis, and hidradenitis suppurativa.

Discussion

Cutaneous HPA-axis and inflammatory pilosebaceous dermatoses

Acne vulgaris

Acne vulgaris is a chronic inflammatory disorder of the PSU characterized by comedones, inflammatory papules and pustules, and occasionally nodulocystic lesions on the sebaceous-rich areas including the face, scalp, chest, and back. The pathogenesis of acne is multifactorial and includes increased follicular corneocyte adhesion, sebum production, and perifollicular inflammation promoted by *Propionibacterium acnes* (*P. acnes*), (**Figure 4B**), [31].

Cortisol and acne

Psychological stress leads to various hormonal changes, including increases in serum CRH and cortisol levels [32]. Cortisol is produced by adrenal glands and hair follicles after they are stimulated by CRH [20]. Although studies on direct effects of elevated serum cortisol on acne are lacking, acne exacerbation is associated with both acute and chronic psychological stress [33, 34]. Emotional stress induced by an academic examination led to a significant increase in pustule count compared to counts three weeks prior to the examination and two weeks after examination results were released ($P<0.01$, counts not specified), [34]. This acne exacerbation was associated with an increase in skin surface free fatty acid ($P<0.005$), [34]. Overall, sebocytes can be stimulated by stress reactants, such as CRH, to increase production of sebum and proinflammatory peptides, resulting in acne

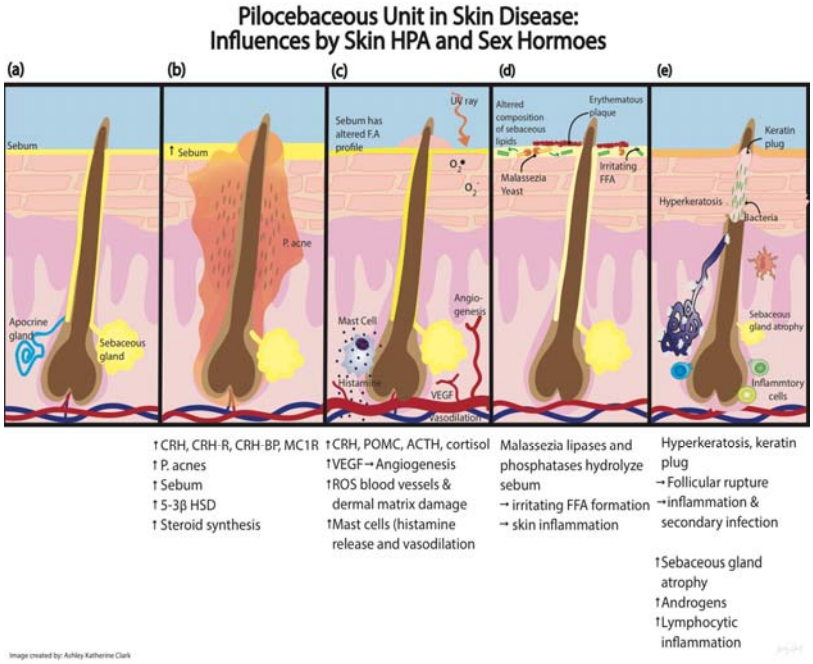

Figure 4. *The role of cutaneous HPA-like axis and steroid hormones on the pilosebaceous unit are depicted for:* ***A)*** *normal skin; representation of normal pilosebaceous unit and sebum.* ***B)*** *Acne vulgaris; psychological stress leads to various changes, including increase in serum CRH, CRH-R, CRH-BP, MC1R, and cortisol levels. Sebocytes are stimulated by stress reactants, such as CRH, to increase production of sebum and proinflammatory peptides, resulting in acne formation and exacerbation. Androgens bind to sebocytes and stimulate an increase in sebum synthesis providing an ideal environment for P. acnes proliferation. The pathogenesis of acne is multifactorial and includes increased follicular corneocyte adhesion, sebum production, and perifollicular inflammation promoted by Propionibacterium acnes (P. acnes), as demonstrated here.* ***C)*** *Rosacea; UV radiation leads to generation of reactive oxygen species (ROS) in the skin, which damage blood vessels and dermal matrix. Additionally, UV radiation stimulates the cutaneous HPA-axis to increase CRH, POMC, ACTH, and cortisol production. CRH in turn activates mast cells, resulting in increased pro-inflammatory cytokines IL-6 and IL-8 (manifests as facial erythema), and histamine release causing vasodilation (manifests as skin flushing and warmth). The increase in vascular endothelial growth factor (VGEF) is responsible for angiogenesis in rosacea. These dermal changes are associated with altered sebaceous fatty acid composition.* ***D)*** *Seborrheic dermatitis; Seborrheic dermatitis is associated with Malassezia overgrowth, which leads to alteration of sebaceous fatty acid composition, rather than the total quantity of sebum. Specifically, the Malassezia lipases and phosphatases hydrolyze sebum, which results in irritating FFA formation and skin inflammation. This manifests as erythematous patches and plaques with greasy scale affecting SG rich locations.* ***E)*** *Hidradenitis suppurativa; In HS, androgens induce hyperkeratosis, which leads to follicular occlusion by the keratin plug. This follicular occlusion ultimately leads to follicular rupture, inflammation, and secondary infection. Although some individuals with HS may have elevated androgen levels, not all do. It is hypothesized that increased peripheral receptor sensitivity to sex hormones, rather than total serum sex hormone levels, contributes to HS. IGF-1 is likely responsible for this increased androgen receptor sensitivity. HS is also associated with increased sebaceous gland atrophy. 5-3β-HSD, Δ5-3β-hydroxysteroid dehydrogenase; CRH-BP, CRH-binding protein; CRH-R, CRH-receptor; MC1R, melanocortin-1-receptors; ROS, reactive oxygen species.*

formation and exacerbation [35, 36]. Since cortisol is a stress hormone and acne is believed to worsen intimes of stress, it is likely that cortisol plays a role in acne development and exacerbation. However, the mechanism by which cortisol may be associated with acne is unclear and studies evaluating serum cortisol levels in individuals with acne are necessary.

Androgens and acne

During puberty, sex hormones trigger SG activation, leading to excess sebum production [25], a key factor in follicular adhesion and acne vulgaris pathogenesis. Androgens bind to sebocytes to stimulate sebogenesis [37] providing an ideal environment for *P. acnes* proliferation [31]. Dehydroepiandrosterone sulfate stimulates sebum production in men and women, as well as acne development in prepubertal girls [38]. Elevated serum androgen levels are associated with severe nodular acne in both sexes. However, although androgens enhance sebogenesis, they are not the only endocrine stimulus for acne development. Individuals with mild to moderate acne may have normal serum androgen levels, highlighting the influence of end-organ receptor sensitivity [39]. Vora et al. showed that serum IGF-1 levels correlate with facial sebum secretion rate in individuals with acne vulgaris [40]. Acne severity correlates with serum levels of IGF-1, but not with serum androgens, which persist at high levels after puberty despite the decrease in acne after puberty [41, 42]. Interestingly, patients with Laron syndrome who have a congenital IGF-1 deficiency exhibit functional androgen receptors but do not develop acne, unless supplemented with high doses of recombinant IGF-

1, which suggests that IGF-1 and androgen interaction are needed for acne development [43].

Estrogens and acne

Estrogens suppress androgen production and SG size and function [41], which in turn improves acne. A higher dose of estrogen is needed to suppress SG function than ovulation [44]. Estrogens are believed to oppose the effects of androgens within SG by reducing sebum synthesis, inhibiting gonadal tissue androgen production, and regulating genes involved in SG growth [44].

Acne therapies and their cutaneous targets

Various hormonal therapies have been used for acne treatment. Anti-androgens inhibit the ovarian and adrenal androgen production, as well as androgen-metabolizing enzymes in the PSU [44]. Androgen receptor blockers include spironolactone, cyproterone acetate, and flutamide. Spironolactone inhibits sebogenesis by blocking androgen receptor function and androgen production by inhibiting 5-α-reductase [45, 46]. Spironolactone is a commonly used hormone-modulating therapy for adult female acne. Most patients using spironolactone experience improvement in their acne within three months [45].

Cyproterone acetate is an androgen receptor blocker that competes with androgens for its receptor [47]. In Europe, cyproterone acetate is combined with ethynyl estradiol into an oral contraceptive that is approved for acne treatment. Generally, oral contraceptive pills (OCPs) reduce ovarian androgen production, as well as sebum production [44].

Combined OCPs contain progesterone and estrogen; the latter increases synthesis of sex hormone binding globulin (SHBG) which binds to and reduces the level of free circulating testosterone [48]. For this reason, combined OCPs are more effective than progesterone-only therapies in treating acne [48].

Isotretinoin (13-*cis*-retinoic acid) is an oral retinoid and the most effective therapy for severe, recalcitrant acne [49]. Isotretinoin decreases the skin androgen receptor expression and suppresses DHT production [50] resulting in reduced sebogenesis and the overall SG size [51]. Additionally, isotretinoin induces sebocyte apoptosis [52, 53]. Furthermore, isotretinoin reduces serum levels of pituitary hormones [54] and hepatic synthesis of IGF-1 [55].

Rosacea

Rosacea is a common chronic inflammatory skin disease consisting of several subtypes that are characterized by persistent centrofacial erythema with periods of trigger specific intensifications and facial phymatous changes [56, 57]. Facial flushing, telangiectasias, inflammatory papules and pustules, facial burning/stinging sensation, skin dryness, edema, and ocular manifestations are characteristics of rosacea [58]. Although its pathogenesis is poorly understood, the key contributing mechanisms include climatic exposures, vascular dysfunction, PSU abnormalities, matrix degeneration, microbial overgrowth, and emotional and physical stressors [59, 60]. TRPV1 are cell receptors in the skin that are activated by rosacea triggers such as spicy food, heat, and alcohol and are associated with neurovascular dysregulation in rosacea [61]. Furthermore, these triggers cause misfolded protein accumulation in the endoplasmic reticulum (ER) to cause ER stress [62], which leads to increased cathelicidin production (antimicrobial peptide) and elevated proinflammatory and angiogenic signaling, all of which are pathogenic factors of rosacea [62].

The papulopustular rosacea (PPR) subtype is associated with altered sebaceous fatty acid composition, with normal total sebaceous fatty acid quantity. Altered sebaceous lipid composition is likely responsible for the skin barrier dysfunction in rosacea [63]. *Demodex* mites are a normal part of skin microbiome and abundant within the PSU on the face. However, individuals with rosacea tend to have significantly higher numbers of *Demodex* mites compared to healthy controls [64].

Cortisol and rosacea

UV radiation stimulates the cutaneous HPA-axis to increase the production of CRH, POMC, ACTH, and cortisol (**Figure 4C**), [65]. Corticotropin releasing hormone activates mast cells leading to increased levels of proinflammatory cytokines IL-6 and IL-8, which manifests as facial erythema [66]. Mast cells also release histamine to cause vasodilation [66], which manifests clinically as skin flushing and warmth. Disturbance of corticosteroid homeostasis

also plays a major role in manifestation of rosacea [67]. Emotional stress activates the HPA-axis to increase cortisol release, which activates inflammatory pathways and impairs the skin barrier function [68]. In a survey conducted by the National Rosacea Society (NRS), emotional stress was reported as one of the most common rosacea triggers, affecting 79% of respondents [69]. In a similar survey by the NRS, 69% of individuals with rosacea reported that emotional stress was associated with monthly rosacea exacerbation [69]. Drake et al. reported that 67% of patients can reduce rosacea exacerbations by focusing on stress reduction alone [69]. This survey did not differentiate between the different subtypes of rosacea. The mechanism for how emotional stress causes vasodilation and flushing remains unclear and may relate to histamine release as a result of elevated CRH.

Androgens and rosacea

Schmidt et al. reported no difference in androgen and estrogen receptor distribution or receptor levels between rosacea-affected skin and normal skin of the same patients [70]. Additionally, serum levels of sex steroids, androgen and estrogen, were within normal range. These findings suggest that sex steroid receptor distribution and serum hormone levels may not be involved in rosacea pathogenesis. The role of peripheral receptor sensitivity also remains unknown.

Estrogen and rosacea

Zaun et al. reported that corticosteroid mediated side effects on the skin, such as telangiectasias, rosacea, and striae are potentiated by estrogens [71]. Estrogen regulates the production of vascular endothelial growth factor (VEGF), which is responsible for angiogenesis [72]. VEGF promotes vascular leak and permeability and is sometimes referred to as the "vascular permeability factor" [73]. Notably, there is some evidence suggesting that estrogen alters the vaginal microbiome [74]. Its role in altering the facial skin microbiome, including *Demodex*, remains unclear.

Rosacea management

The first line management of rosacea includes avoidance of stressors, such as sun exposure, and utilizing adequate sun protection and moisturizing measures. Meditation and yoga are believed to act on the HPA-axis leading to reduced cortisol level [68] and are therefore recommended for emotional stress reduction. Unlike acne, hormonal therapy is not a component of rosacea treatment.

Isotretinoin is a commonly used therapy for recalcitrant and inflammatory rosacea [51]. As mentioned previously, isotretinoin decreases the skin androgen receptor levels and suppresses DHT production [50], resulting in reduced sebogenesis and SG size [51]. Additionally, isotretinoin reduces facial cutaneous blood flow [51]. In a study among 22 patients with treatment resistant rosacea, 10mg of isotretinoin daily for four months led to a significant decrease in inflammatory papules, pustules, erythema, and telangiectasia [75]. As mentioned previously, sebocytes produce abundant amounts of cathelicidin, an antimicrobial peptide and crucial ER-stress induced effector of rosacea pathogenesis [76]. Isotretinoin causes sebocyte apoptosis, resulting in decreased production of sebum and cathelicidin [77].

Topical ivermectin 1% cream is an approved rosacea therapy that has dual anti-inflammatory and antiparasitic properties [78]. It leads to a reduction of *Demodex* mites in the skin and reduces the expression of proinflammatory cytokines, including IL-8, leading to improvement in clinical signs of rosacea [78].

Seborrheic dermatitis

Seborrheic dermatitis (SD) is an inflammatory condition characterized by both poorly and sharply demarcated, pink to erythematous patches and plaques with greasy scale affecting SG rich locations, such as the scalp, ears, face, and chest. The etiology is not completely understood but is considered to be associated with *Malassezia* overgrowth [79] and metabolism of sebaceous lipids, leading to altered sebaceous fatty acid composition, rather than the total quantity of sebum (**Figure 4D**), [80]. Lipases and phosphatases of *Malassezia* hydrolyze sebaceous lipids, breaking down triglycerides into free fatty acids (FFA), [80]. Certain FFA byproducts, such as oleic acid, cause skin irritation and a subsequent inflammatory response that is seen in SD

[80]. FFAs, such as palmitic and oleic acid, are also danger signals that stimulate toll-like receptor 2 (TLR2), which activates the NLRP3 inflammasome [81]. Thus, isotretinoin-mediated sebum suppression may suppress sebaceous lipid-mediated proinflammatory effects.

Cortisol and seborrheic dermatitis
Misery et al. conducted a prospective survey study among 82 subjects with SD [82]. The majority reported stress as the main trigger of their disease [82]. However, our search did not result in any studies on the relationship between cortisol and SD. Future studies on this topic are needed.

Androgens and seborrheic dermatitis
No specific association between androgens and SD has been identified. However, SD begins at puberty and is more common in men than women suggesting that androgens may be implicated in SD pathogenesis [83]. Furthermore, seborrheic dermatitis may coincide with acne, supporting the idea that it is associated with oily skin [83] and that androgens may be the contributing factor.

Estrogen and seborrheic dermatitis
There is no evidence directly linking estrogen to SD. However, emerging evidence reveals that estrogen may affect the fungal microbiome (mycobiome), [84]. A study on castrated rats showed that those treated with an intravaginal estrogen challenge are susceptible to *Candida albicans (C. albicans)* colonization, whereas untreated rats remained resistant to yeast colonization [85]. Estrogen is considered to be one of the main factors influencing the pathogenicity of *C. albicans* in the vaginal environment [86, 87]. Although studies on estrogen and *Malassezia* are lacking, these data raise the possibility that estrogen may alter the skin mycobiome and contribute to SD development.

Seborrheic dermatitis management
Although hormonal therapy is not a component of SD management, isotretinoin affects the steroidogenesis pathway, as described in previous sections. In doing so, isotretinoin leads to decreased sebum production. Although altered sebaceous profile is the culprit for SD development rather than increased sebogenesis, isotretinoin is an effective treatment of refractory seborrhea and SD affecting the face and scalp [88]. In a randomized comparative trial involving 45 adults with refractory seborrhea or SD, patients who received isotretinoin (10mg every other day for six months) had significantly greater sebum reduction than subjects who received antiseborrheic topical therapy (shampoo for the scalp and soap for the face for six months), [88]. Patient opinion, investigator evaluation, and quality of life assessments improved in both groups. This study demonstrated that isotretinoin might be an effective alternative for SD treatment in individuals resistant to standard therapies. Further studies are needed to determine the exact mechanism by which isotretinoin improves SD.

Hidradenitis suppurativa (HS)
Hidradenitis suppurativa (HS) is a chronic, painful, and debilitating inflammatory skin condition that affects apocrine gland bearing areas, such as the axilla, inframammary folds, and groin [89]. The characteristic findings are painful nodules, sinus tracts, and scaring [90, 91]. HS typically develops after puberty [89]. Women are more prone to HS than men. However, men typically have a more severe form of HS [92]. Pathogenesis of HS remains controversial. It was long thought that the condition results from apocrine gland abnormality [91], but emerging evidence suggests that follicular structural fragility with subsequent aberrant adaptive immunity plays a major role [93]. IL-12, IL-23, and TNF are strongly implicated in HS pathogenesis [94, 95]. Furthermore, HS is associated with metabolic syndrome [96] and inflammatory bowel disease (Crohn disease), [96-98], suggesting a chronic inflammatory state.

Cortisol and hidradenitis suppurativa
There is currently no evidence linking psychological stress or cortisol level to the development of HS.

Androgens and hidradenitis suppurativa
HS flares are associated with the menstrual cycle and acne vulgaris, thus sex hormones likely play a role in HS pathogenesis [90, 99]. Androgens may contribute to HS pathogenesis as suggested by pre-menstrual flare-ups and symptom improvement during pregnancy [91, 100]. Follicular occlusion secondary to hyperkeratosis is an inciting event in HS and is

induced by androgens (**Figure 4E**), [101, 102]. However, in a systematic review of 59 studies, Riis et al. concluded that individuals with HS did not have elevated serum sex hormones levels [90]. Similarly, Harrison et al. enrolled 13 women with premenstrual HS flares and nine healthy controls to study the downstream hormonal response to stimulation by gonadotropin releasing hormone (GRH), (200 micrograms) and thyrotropin releasing hormone (TRH), (200 micrograms), [100]. Serum levels of various hormones were measured at baseline and 10, 20, and 60 minutes after challenge. There were no significant differences in the levels of estrogen, progesterone, total testosterone, and DHEAS at any time point between the two cohorts. Despite being an androgen-driven disorder, elevated total serum testosterone level is not the root cause. Increased target organ conversion of androgens to active metabolites likely contributes to HS pathogenesis [100].

Furthermore, it has been theorized that increased peripheral receptor sensitivity to sex hormones, rather than total serum sex hormone levels, contributes to HS. IGF-1 is likely responsible for this increased androgen receptor sensitivity. Specifically, high glycemic load and high dairy consumption, as is seen in a Western diet, lead to increased hepatic synthesis of IGF-1 and a resulting increase in androgen receptor exposure to circulating androgen hormones [103, 104]. Diets that limit dairy and high glycemic index foods are believed to prevent HS progression [105].

Estrogen and HS

Serum estrogen regulates CRH function and acts on estrogen receptors within SG to suppresses SG activity [6]. There is no difference in the number of estrogen receptors found in apocrine glands in skin biopsies of individuals with HS compared with healthy skin [6]. However, HS is rare in menopausal women correlating with decline of estrogen levels, but the exact relationship between estrogen and HS has yet to be determined [6, 90].

HS management

Spironolactone has provided HS relief in some individuals. In a retrospective, single center electronic database review study in Australia, 20 women with HS who were treated with

Table 1. *Summary of inflammatory pilosebaceous dermatoses management.*

Disease	Management	Mechanism of action
Acne vulgaris	Spironolactone	Inhibits 5-α-reductase Blocks androgen receptor function
	Cyproterone acetate	Competitive inhibitor of androgen receptor
	Flutamide	Androgen receptor blocker
	Combined oral contraceptive pills	Anti-androgenic (Increases SHBG and reduces free circulating androgens)
	Isotretinoin (13-*cis*-retinoic acid)	Reduces skin androgen receptor expression Suppresses DHT production Induces sebocyte apoptosis Reduces serum levels of pituitary hormones Reduces hepatic synthesis of IGF-1
Rosacea	Isotretinoin	Reduces skin androgen receptor expression Suppresses DHT production Induces sebocyte apoptosis Reduces facial cutaneous blood flow
Seborrheic dermatitis	Isotretinoin	Reduces sebum production (Exact mechanism in SD unknown)
Hidradenitis suppurativa	Spironolactone	Inhibits 5-α-reductase Blocks androgen receptor function
	Finasteride	Blocks conversion of testosterone to DHT Reduces sensitivity of PSU to androgen stimulation
	Combined oral contraceptive pills	Anti-androgenic (Increases SHBG and reduces free circulating androgens)

spironolactone showed significant improvement in disease severity measured by Physical Global Assessment (PGA). The authors suggested that spironolactone should be first-line therapy in mild to moderate HS [106]. However, the quality of this study is limited by small sample size, retrospective design, and single center data. Larger and better-designed studies are needed to evaluate the efficacy and safety of spironolactone as a treatment for women with HS.

Finasteride exerts its anti-androgen effects by both blocking the conversion of testosterone to DHT and decreasing sensitivity of the PSU to androgen stimulation [107]. Finasteride may be a helpful therapy for HS and has a favorable safety profile [107]. In a case series of three pediatric patients with HS, finasteride reduced the frequency and severity of HS flares and caused no significant side effects [108]. Among seven adults with HS, six achieved significant improvement and three achieved complete healing of HS lesions [109]. Finasteride was well tolerated; one subject experienced generalized pruritus without a rash, whereas two female subjects reported breast enlargement [109]. Owing to risk of teratogenicity (Pregnancy Category X), reliable contraception is needed if finasteride is used in women of childbearing age.

Oral contraceptives have been used to treat HS. When used over a 12-month period in women with HS, ethinyloestradiol /cyproterone acetate 50mg and ethinyloestradiol 50 micrograms/norgestrel 500 micrograms both significantly reduced active circulating androgens and increased SHBG [110]. Additionally, HS cleared completely in 29% of subjects. These results suggest that anti-androgen therapy is beneficial in treating HS.

Conclusion

The cutaneous HPA-axis responds to endogenous and exogenous stressors in order to maintain local homeostasis. Corticotropin releasing hormone, ACTH, MSH, and cytokines are implicated in the regulation of the cutaneous HPA-axis and local steroidogenesis. Cutaneous HPA-axis dysregulation is involved in the development of inflammatory pilosebaceous disorders, including acne, rosacea, and HS. The role of steroid hormones and seborrheic dermatitis is least well characterized of these diseases. Additional studies are needed on the skin stress response system and its contribution to the development of inflammatory dermatoses. Steroid hormones play a role in inflammatory dermatoses and targeting cutaneous steroidogenic activity may be helpful in uncovering new therapeutic strategies (**Table 1**).

Potential conflicts of interest

The authors declare the following potential conflicts: RKS serves as a scientific advisor to Dermveda. VYS, SSB, and AKC have no conflicts of interest.

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