Clinics in Dermatology (2017) **35**, 130–137

ELSEVIER

Clinics in Dermatology

Sex hormones and acne

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Abstract The skin is an endocrine organ with the expression of metabolizing enzymes and hormone receptors for diverse hormones. The sebaceous gland is the main site of hormone biosynthesis, especially for androgens, and acne is the classical androgen-mediated dermatosis. In sebocytes, conversion of 17-hydroxyprogesterone directly to dihydrotestosterone bypassing testosterone has been demonstrated, while type II 17β-hydroxysteroid dehydrogenase can inactivate the action of testosterone and dihydrotestosterone. The androgen receptor–dependent genomic effect of dihydrotestosterone on sebocytes is confirmed. Further evidence supports the PI3 K/Akt/FoxO1/mTOR signaling in the involvement of the interplay between androgens, insulin, insulin-like growth factor, and hyperglycemic diet in acne. Androgens not only regulate embryology and lipogenesis/sebum synthesis in sebocytes but also influence inflammation in acne. Genetic studies indicate that regulation of the androgen receptor is an important factor in severe acne. Further studies are required to understand the effect of estrogen and progesterone on sebaceous gland and comedogenesis, considering the change of acne in pregnancy and postmenopausal acne. Special attention should be paid to nonobese patients with polycystic ovarian syndrome and hyperandrogenism-insulin resistance-acanthosis nigricans syndrome. In spite of extensive gynecologic experience in the use of combined oral contraceptives for acne, evidence based on dermatologic observation should be intensified.

Introduction

The skin can be considered as an endocrine organ, because it has been shown to be able to synthesize diverse hormones with expression of the associated hormone receptors.[1,2]

Sex hormones can be broadly divided into three groups, based on chemical structure and clinical relevance: Sex

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http://dx.doi.org/10.1016/j.clindermatol.2016.10.004
0738-081X/

steroids androgen, estrogen, and progesterone; glycoprotein hormones luteinizing hormone, follicle-stimulating hormone, gonadotropin-releasing hormone, and human chorionic gonadotropin; and peptide hormones such as prolactin and oxytocin. Apart from androgen, the pathogenic role of other hormones in dermatology is much less defined.

The sebaceous gland is the major site of steroid synthesis in human skin. In the classic androgen biosynthetic pathway, testosterone (T) is produced from DHEA and androstenedione/-diol in the gonads as well as in the skin, via the action of 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-HSD. T is regarded as an essential intermediate in sex steroid synthesis, which can be further converted to estradiol (E2) by aromatase or to 5α-dihydrotestosterone (DHT) by 5α-reductase.

Acne is the classic example among androgen-mediated skin the diseases where the pathogenic role of androgen is best studied. Sebaceous gland is equipped with all the necessary enzymes for the synthesis and metabolism of androgen from cholesterol to DHT. Expression of androgen receptor (AR), estrogen receptor especially ERα, and progesterone receptors, especially PRB, has been demonstrated in the sebaceous gland.[3,4]

In this review, we are to focus on sex steroids and will summarize and discuss the most recent major findings related to acne in our view over the past 5 years.

Physiology

Biosynthesis and metabolism of sex hormones: androgen, estrogen, and progesterone

The cloning of many estrogen-specific 17β-HSDs and the observation of higher affinity of aromatase and 5α-reductase for 4-androstenedione than T strongly suggest that the synthesis of E2 and DHT can bypass T. A study of mutations in AKR1 C2/4 genes encoding for 3α-HSDo identified this novel, alternative, backdoor pathway for DHT synthesis in fetal testis in 46,XY individuals with gonadal insufficiency, where 17-hydroxyprogesterone can be directly converted to DHT by 5α-3α reductive steps.[5] This biosynthetic pathway has also been demonstrated in the cultured SZ95 sebaceous gland.[6,7] The clinical significance of the synthesis of DHT independent of T remains to be determined.

Detection of the immunoreactivity of 3β-HSD1, CYP11 A1, steroidogenic acute regulatory protein, 17β-HSD5, CYP17 A1, 5α-red1, PRB, AR, and NGFI-B in normal human sebaceous gland lends further evidence for the *in situ* androgen and progesterone synthesis.[4,8] An exclusive expression of 17β-HSD2 in sebaceous glands was found to be negatively correlated with that of peroxisome proliferator-activated receptor gamma (PPARγ). Overexpression of 17β-HSD2 will inhibit the synthesis of T and DHT in SZ95 sebocytes.[9] In human skin, the *in situ* expression levels of aromatase and steroidogenic acute regulatory protein were positively correlated with estrogens and T concentrations, respectively.[10] Inactivation, of estradiol is primarily mediated by estrogen sulfotransferase in normal epidermal keratinocytes, whereas significant induction of estrogen sulfotransferase activity was observed in differentiated keratinocytes, indicating suppression of estradiol action in epidermal differentiation.[11] Aldo-keto reductase 1 C3, which mediates the metabolism of sex hormones, especially the inactivation of progesterone and DHT, has been demonstrated in differentiated suprabasal epidermis.[12] So far, none of the sex hormones inactivating enzymes, including UDP-glucuronosyltransferases, were found in the sebaceous glands.

Receptors: expression and function

Androgens can act through nongenomic and AR-dependent genomic mechanisms. In a stable human sebocyte cell line constitutively expressing a fully functional AR, DHT alone has been demonstrated for the first time to be able to drive immature sebocytes in a clear lipogenic differentiation process.[13] Estrogen was shown to induce rapid change in the cell morphology and cytoskeleton organization of skin fibroblast via a nongenomic mechanism through the nonclassical G protein–coupled receptor GPR30 and ERK1/2 activation.[14] The nongenomic effect of androgens and other sex steroids via steroid-induced modulation of cytoplasmic or cell membrane–bound regulatory proteins remains unknown in sebocytes.

In the adult mouse, epidermal development and homeostasis is determined by reciprocal activation between AR and Wnt/β-catenin signaling. AR activation reduced β-catenin-dependent transcription, blocked β-catenin-induced induction of hair growth, and prevented β-catenin-mediated conversion of sebaceous glands into hair follicles. Conversely, AR inhibition enhanced the effects of β-catenin activation, promoting hair follicle proliferation and differentiation, leading to a complete loss of sebaceous gland identity.[15] Overexpression of c-MYC stimulated sebaceous differentiation, which was reduced in mice lacking a functional AR and could be restored by treatment with T or p53 deletion via activation of AR signaling.[16]

Interaction with insulin and insulin-like growth factor

It is hypothesized that a high-glycemic-load diet can increase insulin-like growth factor (IGF-1) and insulin and induce acne by reducing nuclear localization of the forkhead box-O1 (FoxO1) transcription factor via activation of the phosphoinositide-3-kinase (PI3 K)/Akt pathway.[17] The PI3 K/Akt/FoxO1 pathway was recently demonstrated in cultured SZ95 sebocytes and its stimulation was associated with a significantly reduced proliferation but increased differentiation of sebocytes, to a greater extent by IGF-1 than by insulin.[18] DHT induces SREBP-1 expression and lipogenesis in HaCaT cells via activation of the PI3 K/Akt pathway.[19]

In patients with acne, compared with the controls, a significantly higher serum IGF-1 level, greater expression of FoxO1 in cytoplasm than in nucleus, and more intense expression of

mTOR were observed.[20] A significant association between IGF-I (CA) polymorphism and severity of acne was suspected,[21] although acne was observed in only one of a total of 21 cases at full puberty with Laron syndrome, characterized by congenital IGF-1 deficiency.[22] Among the eight patients treated with IGF-1 at 70-200 μg/kg/day, acne was not observed in two male patients but observed in three of the six female patients, which disappeared by reduction of the IGF-1 dose to 50 μg/kg/day or cessation of treatment, supporting the interaction between sex steroids and IGF-1 in acne pathogenesis.

Pathogenesis

The exact mechanisms of sex steroids in acne pathogenesis remain unclear. Although the androgenic effect of DHT is more potent than that of T *in vitro*, the difference in their effect on acne is unclear. Serum circulating androgen levels, progesterone, glucocorticoids, insulin, and IGF-1 are known to be elevated in patients with acne vulgaris, but serum estradiol levels and sex hormone binding globulin (SHBG) are lower than those in controls.[23,24] In nonobese nonhirsute women, higher values of free T and SHBG with lower levels of estradiol were significantly in favor of severe acne, which again was associated with higher values of cholesterol and LDL-C and lower values of HDL-C and ApoA-1 levels.[25] Clinical observation of cross-sex hormone therapy in trans-persons suggested that T is the main player compared with estrogen and progesterone in acne.[26]

Action of androgen, estrogen, and progesterone on comedogenesis

Earlier studies showed that 5α-reductase was expressed and more active in the follicular infrainfundibulum,[27] indicating the possible action of androgen on comedogenesis. Further studies are lacking.

The FGFR2 gain-of-function mutations in Apert syndrome and unilateral acneiform nevus can be used to study androgen-dependent FGFR2-signaling in acne[28]; however, a direct demonstration of FGFR2 expression in human sebaceous glands and hair follicle infundibulum is so far lacking. The loss of sebaceous glands was found to be associated with the formation of comedones in chloracne.[29]

Despite the benefit of combined oral contraceptives (COCs) for acne, data about the effect of estrogen and progesterone on acne, in particular comedogenesis, are very limited. Estrogen is supposed to act antiandrogenic or sebosuppressive, either directly or indirectly.[30] The influence of progesterone seems to be more complicated in acne, because perimenstrual changes correlate with peak levels of progesterone, but natural and artificial progesterones display both antiandrogenic activity and androgenic activity.[31] Postmenopausal occurrence of closed comedones deserves further attention.[32] Hormone replacement therapy may serve as a good model for study of the effect of estrogen and progesterone on the pilosebaceous unit.

Action of androgen, estrogen, and progesterone on sebum production and acne severity

It is known that the appearance of acne in prepubertal girls and sebum production in both sexes correlate with serum DHEA levels.[33] A higher serum level of progesterone but lower estrogen was found in patients with acne vulgaris.[23] COCs containing ethinyl estradiol and various progestins can inhibit sebum secretion from face and scalp,[34] whereas postmenopausal estrogen replacement therapy increases sebum production.[35] A few studies address the changes of acne during pregnancy, with inconsistent findings.[36,37] Direct evidence of the effect of estrogen and progesterone on sebum production is lacking.

Human facial skin can be categorized as T-zone with high levels of sebum secretion and as U-zone with low levels of sebum secretion. The results of *in vivo* topographic analysis indicated a statistically significant increased AR expression in the sebaceous glands in the T-zones than in the U-zones.[38] *In vitro* experiments using human primary sebocytes also yielded similar results, with higher levels of AR protein and mRNA expression in T-zones.

PPARβ/δ has prodifferentiating effects in keratinocytes, regulates sebocyte differentiation, and promotes hair follicle growth in healthy skin.[39] Expression of PPARβ/δ is significantly higher in patients with acne than in controls, and in lesional than nonlesional skin.[40] Interaction between sex steroids and PPARβ/δ is much less studied.

Genome-wide association studies in Han Chinese identified a susceptibility gene locus 11 p11.2 encoding the damage-specific DNA binding protein 2 (*DDB2*), which is associated with the degradation of AR and severe acne.[41,42] Genetic polymorphisms of HSD3 B1 and HSD17 B3 were also found to increase the susceptibility to acne vulgaris in Han Chinese.[43] In European Americans with severe teenage acne, a significant association with *MYC*-gene relating to upregulation of AR on the chromosome 8 q24 region was observed.[44]

Action of androgen, estrogen, and progesterone on *Propionibacterium acnes* and inflammation

Acne is considered by some investigators as a chronic inflammatory disease, in which activation by *P acnes* and abnormal sebum plays an important role.[45] Until now, evidence of the direct effect of sex hormones on *P acnes* is very scanty. One early study showed that high doses of T and anabolic steroids might increase the *P acnes* population.[46] It is unclear whether sex steroids can influence the activity of different strains of *P acnes*.[47] DHT was found to be able to upregulate IL-6 and TNF-α in primary sebocyte cultures from the scalp.[48] A complex interaction between IGF-1 and

estrogen was recently demonstrated in skin wound healing, in which the antiinflammatory effects of IGF-1 are predominantly via the ERs, in particular ERα.[49] In diverse disease models of the brain inflammation, estrogen and progesterone are neuroprotective and antiinflammatory, and can attenuate proinflammatory cytokine activity.[50] In gynecologic disorders, such as endometriosis and preterm fetal loss, the inflammation appears to be associated with an imbalance between estrogen and progesterone actions.[51]

Clinical aspects

Acne-associated endocrinologic disorders

Polycystic ovarian syndrome (PCOS), hyperandrogenism-insulin resistance-acanthosis nigricans (HAIR-AN) syndrome, and late-onset nonclassic congenital adrenal hyperplasia (NC-CAH) are classic examples of endocrinologic disorders closely associated with acne.[52]

Polycystic ovarian syndrome

PCOS is prevalent in women with severe acne, late-onset acne, persistent acne, and acne resistant to conventional therapies.[53] The etiology remains unclear, but genetics along with early androgen exposure likely plays a role.[54] Genome-wide association studies identified 16 robust loci for PCOS, with some loci containing genes involved in reproductive (*LHCGR*, *FSHR*, and *FSHB*) and metabolic (*INSR* and *HMGA2*) dysfunction.[55] Genes related to normal-weight insulin resistance and chronic inflammation are of central interest for PCOS pathomechanisms,[56] whereas *DENND1 A* plays a key role in the regulation of increased androgen biosynthesis in ovarian theca cells.[57]

So far there are no uniform diagnostic criteria for PCOS, and the Rotterdam classification is the most widely used. The definition proposed in 2003 is obsolete when using the latest generation of ultrasound machines.[58] The definition of biologic hyperandrogenism is still unresolved. The criteria used to define oligo-/anovulation are insufficient. The serum anti-Müllerian hormone assay seems to be a promising surrogate for follicular count and is likely to emerge as the official morphologic marker.

Antiandrogens, including COCs, are effective treatment for acne and hirsutism, whereas lifestyle modification, BMI reduction, and insulin-sensitizing drugs such as metformin benefit acne more than hirsutism. Individual cardiovascular risk should be assessed before starting any estrogen/progestin treatment, and spironolactone is best avoided in women who have a family history of breast cancer,[59] given the large epidemiologic studies failed to prove the association.[60] Lower serum vitamin D levels were found to relate to metabolic and hormonal disorders in women with PCOS[61]; however, it remains to be determined whether vitamin D supplementation can improve the symptoms of PCOS, especially the cutaneous hyperandrogenism.

HAIR-AN syndrome

HAIR-AN syndrome is characterized specifically by the presence of AN and highlights the interaction of androgen and insulin in disease pathogenesis. The assumption that HAIR-AN syndrome is a subtype of PCOS is oversimplified. In our view, this is a heterogenous disease of different etiologies although the definition of the disease is rough. Among the clinical manifestations of hyperandrogenism, hirsutism is more specific and representative, whereas acne severity and hair loss are varying and in need of a better definition. We suspect that there is a rare idiopathic form without obesity, PCOS, or hyperandrogenemia. The higher serum levels of pigment epithelium–derived factor and fibroblast growth factor (FGF) 21 in obese patients with AN than those without AN indicate that factors additional to insulin resistance should be considered.[62,63] Attention should also be paid to the AN-associated syndromes and their genetic mutations, such as Rabson-Mendenhall syndrome, Alström syndrome, Donohue syndrome, Berardinelli-Seip syndrome, Costello syndrome, aromatase deficiency syndrome, MORFAN (mental retardation, pre- and postnatal overgrowth, remarkable face, and acanthosis nigricans) syndrome, SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans) syndrome, and Crouzon syndrome.

Nonclassic congenital adrenal hyperplasia

In NC-CAH, cortisol production is normal but with excessive precursor accumulation to overcome the partial enzyme deficiency, leading to the characteristic elevation of 17-hydroxyprogesterone and more specifically 21-deoxycortisol in a very low amount.[64] A high rate of genotype-phenotype discordance has been found in 21-hydroxylase deficiency.[65] Although a higher frequency of V281 L/V281 L, I2 G/V281 L, and Del/V281 L mutations of CYP21 A2 was found in NC-CAH,[66] genotypic grading of CYP21 A2 did not correlate with the severity of cutaneous manifestations.[67,68] Other contributing factors such as the CAG repeat length of the *AR* gene have been demonstrated.[69] In the absence of *CYP21 A2* gene mutations, mutations in the *CYP11 B1* gene associated with steroid 11β-hydroxylase deficiency should be examined.[70] Screening of NC-CAH in women with severe adult acne is warranted.[71]

Treatment remains controversial, particularly in boys and men, and no universally accepted guidelines have been established.[72] The aim is to correct the hyperandrogenemia without suppression of endogenous cortisol production.[64] Ultralow-dose dexamethasone (0.025 mg/day) at night was reported to be a promising strategy.[73] More evidence is needed to see whether the use of glucocorticoid is indispensable, when antiandrogens or oral isotretinoin would suffice in the treatment of cutaneous manifestations in women.

Obesity, sex steroids, and acne

Epidemiologic studies from different regions further support the association between obesity and acne in adolescents,[74–76] which is less evident regarding boys,[77] and inconsistent in adult women.[78] Differential analysis of obese versus nonobese women with or without PCOS may help to answer the question. The androgenic effect on obesity seems more complex in men. A bidirectional relationship between T and obesity is indicated by the hypogonadal-obesity cycle and that weight loss can lead to increased T levels.[79] The low total T and SHBG levels in the aging men associated with increased central adiposity are associated with the hyperinsulinism and increased inflammatory cytokines accompanying obesity.[80] Sex-specific difference in metabolic homeostasis, the local biosynthesis/metabolism, and intracrine/paracrine action of sex steroids in adipose tissue should be considered in the future research on this topic.[81] To study the interaction between sex steroids and adipokines on sebocyte cultures would be an appropriate *in vitro* model.[82,83]

Antiandrogens in the treatment of acne: benefits and risks

Based on chemical structure and working mechanism, antiandrogens can be classified into three groups: COCs, AR blockers, and enzyme inhibitors. Modern progestins and spironolactone antagonize androgenic action in multiple aspects. Although antiandrogens, especially COCs, are widely used by gynecologists to treat mild to moderate acne, the evidence is generally weak and comparison studies are scanty.[84] Acne associated with endocrinologic disorders, most commonly PCOS, the presence of hirsutism and truncal acne, and adult acne/acne tarda obviously benefit from antiandrogen treatment.

Combined oral contraceptives

Our own experience is in line with the results of a recent meta-analysis showing that systemic antibiotics may be superior at 3 months, whereas COCs are more proper for long-term treatment beyond 3 months.[85] Not only does the newer generation of COCs decrease androgen production in ovary and increase SHBG, thus reducing circulating free T, but it can also reduce 5α-reductase activity and directly block AR partially; however, it is unclear whether different progestins, physiologic estradiol valerate versus the traditional synthetic ethinyl estradiol, or monophasic versus multiphasic, show therapeutic superiority in acne, also in terms of noninflammatory versus inflammatory form.[86,87] Very limited data address the effect of transdermal patch or vaginal ring compared with oral form in acne treatment.[88] We have often observed an exacerbation of acne after change from COCs to contraceptive vaginal rings, but this may be biased by the different composition of the active ingredients.

The most discussed and serious side effects of COCs are potential venous thromboembolisms and the risk for breast cancer. All the COCs bear certain risk for venous thromboembolism, in average 3.5 times greater (relative risk) in user than in nonuser. It is inconclusive whether the dose of estrogens or the type of progestins augments the risk for thrombosis.[89] The risk of venous thromboembolism is estimated to be similar among the third- and fourth-generation progestins desogestrel, drospirenone, gestodene, and cyproterone acetate, which carry a risk 50-80% higher than that associated with the second-generation progestin levonorgestrel.[90] Smoking (≥15 cigarettes per day) and obesity have been confirmed to be additional strong risk factors.[91,92] Women with hereditary thrombophilias (antithrombin, protein C, and protein S deficiency; factor V Leiden; prothrombin-G20210 A mutation) are discouraged from using COCs, and familial history of venous thromboembolism is usually unreliable for clinical judgment.[93]

Regarding the risk of breast cancer, a significant elevation of the risk was confirmed in a 2013 meta-analysis: Ever versus never use was associated with an odds ratio of 1.08 (1.00-1.17) and the increase in lifetime absolute risk estimated at ~0.89%.[94] According to the International Agency for Research on Cancer, the relative risks were highest for use before first pregnancy or at an early age. In the high-risk group with BRCA1 or BRCA2 mutation, the risks for ovarian and breast cancer appeared to be similar to those reported for the general population[95]; on the other hand, oral contraceptives reduced risks for endometrial cancer and ovarian cancer, and the risk reduction is greater with increasing duration of use and persists for ≥20 years after cessation of use.

AR blockers

Spironolactone is an aldosterone receptor antagonist that can decrease T production, block the binding of T and DHT to AR in the skin, inhibit 5α-reductase, and increase SHBG. Its use is popular in the United States (even off-label) but uncommon in Europe.[60] The evidence level is low to moderate, mostly retrospective, and the effective dose and the benefit-risk ratio for acne are inconsistent. Its use can be considered in cases of adult acne unsuitable for COCs. Monotherapy is accompanied with more side effects. Topical preparations deserve a trial especially in men, as no antiandrogens are available for men to date.[96]

Flutamide is a selective nonsteroidal AR block. A few recent studies demonstrated its long-term efficacy in acne treatment, alone or in combination with COCs.[97,98] A dose between 125 and 62.5 mg seems to possess much lower hepatotoxicity.[99]

Enzyme inhibitors

Aldo-keto reductase 1 C3 (AKR1 C3), also known as type 5 17 β-HSD, plays a pivotal role in the biosynthesis of T and DTH within the prostate. A strong expression of AKR1 C3 was demonstrated in the differentiated suprabasal epidermis and hair bulb epithelium.[12,100] Great effort is being made to develop

potent and selective AKR1 C3 inhibitors,[101] Clinical significance although the clinical significance is unknown.

Oral isotretinoin also shows antiandrogenic effect by reducing circulating total T, luteinizing hormone, prolactin, IGF-1, and IGF-binding protein 3.[102]

Conclusions

The sebaceous gland is a good model to study the effect and working mechanism of sex steroids, in particular androgens. Great progress has been made in the understanding of the androgenic effect on sebocyte differentiation and lipogenesis (sebum synthesis), but less is known regarding comedogenesis. New evidence indicates the interaction between sex steroids and inflammation. The difference between T and DTH in acne remains unclear, and the effect of estrogen and progesterone is much less studied. Genetic studies on acne and acne-associated syndromes such as PCOS, HAIR-AN syndrome, and NC-CAH unravel more potential pathogenic factors. The pathogenic role of obesity and diet and their interactions with sex steroids need further analysis. Design of COCs with reduced risks for venous thromboembolism and breast cancer should benefit those women whose acne is associated with PCOS or where the onset of acne occurred after adolescence.

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