NEWS, VIEWS, & REVIEWS

Cutaneous Hyperandrogenism: Role of Antiandrogen Therapy in Acne, Hirsutism, and Androgenetic Alopecia

Skin as an Endocrine Organ

The historical picture of the skin as a simple end target for hormones has been replaced by a more complex understanding of its role as an independent endocrine organ.[1] The skin possesses full enzymatic capacity for the cutaneous synthesis and metabolism of hormones via cell specific expression of enzymes.[2] Newly synthesized hormones act in a paracrine and intracrine fashion and exert increased local activity independent of systemic levels. This localization of effect has been extensively studied with regard to androgens as a means of understanding how androgen mediated disorders seem to occur even in patients with normal circulating hormone levels. Though cutaneous steroidogenesis is modest, less than 1% of total synthesis, it is this local overproduction and increased receptor sensitivity that have been implicated in androgen-dependent dermatoses.[3-5]

Steroidogenic Activity of Skin

Growing interest in dermato-endocrinology has led to the identification of multiple hormones, receptors and classical steroidogenic enzymes in skin.[5] The on-site synthesis of hormones, termed "intracrinology" is thought to contribute to the cutaneous hyperandrogenism mediating androgen-dependent diseases.[6,7] The skin, especially the pilosebaceous unit, is capable of synthesizing cholesterol *de novo* from acetate and expresses the steroidogenic acute regulatory protein (StAR) which controls the translocation of cholesterol from the outer to inner mitochondrial membrane necessary for the initiation of steroid synthesis. In addition, transcription factors regulating steroidogenesis in classical organs, such as SF-1, DAX-1, and WT-1 have been detected in skin.[4,8] However, skin cells do not typically initiate the process of sex hormone synthesis and are more involved in the peripheral conversion of adrenal prohormones into testosterone and DHT, the main androgens active in skin. This occurs due to expression of key regulatory enzymes by sebocytes, dermal papilla cells and sweat glands, with sebocytes acting as the main regulators of local steroid activity.[9,10] Steroid sulfatase, 3βHSD, 17βHSD3 and 5α reductase are involved in androgen synthesis, whereas 17βHSD2, 3α HSD and aromatase are counter regulators and suppress local activity.[7] The mechanistic significance of these enzymes has yet to be determined and future research lies in designing specific inhibitors of androgen metabolizing enzymes in skin, such as those targeting 5α reductase.

Androgen-Dependent Dermatoses

The clinical association of hyperandrogenism with acne, hirsutism and androgenetic alopecia, and the efficacy of antiandrogen therapy have reinforced the pathogenic role of androgens in these disease states. Testosterone and DHT are the main androgens that interact with the androgen receptor (AR) found on sebaceous glands and the dermal papilla cells of the hair follicle. DHT is peripherally converted from testosterone via 5α reductase, which is found in two isoforms; type I is primarily expressed by sebocytes while type II is expressed in hair follicles.[11,12] Expression of type III 5α reductase was also recently found in sebocyte cell lines, but the physiologic significance is unknown.[11] The prime target of androgens is the pilosebaceous unit, starting with the mediation of vellus follicles into sexual hair follicles and sebaceous glands at puberty. This differentiation is location specific; in the forehead and cheeks androgen excess stimulates sebaceous gland hyperplasia while in the axilla, genitalia and face it leads to terminal hair differentiation.[13,14] The follicular response to androgen stimulation is not consistent and, paradoxically, androgen binding can cause miniaturization of the hair follicle, rather than growth, in the vertex of genetically susceptible individuals. If transplanted to a different site, those vertex hairs will continue to miniaturize, while occipital hairs transplanted to the vertex will maintain their androgen insensitivity.[15,16] This phenomenon, known as 'donor dominance,' emphasizes how the intrinsic sensitivity and distribution of the androgen receptor contributes to disease pathogenesis. The site-specific pattern is proposed to occur due to the activation of different second messengers; IGF-1 induces sexual hair growth while TGFβ exerts an opposite effect and suppresses growth on the genetically predisposed frontal and vertex scalp.[17] In addition, the presence of coactivators of AR in the bald frontal scalp as opposed to the occipital scalp can explain the location specific response of the hair follicle to androgens.

Hormonal Therapy

Therapies designed to suppress the effects of androgen stimulation have been utilized off-label for acne, hirsutism and androgenetic alopecia. Only combined oral contraceptives (COC) have been FDA approved for acne, but other agents are widely used in clinical practice as well. Table 1 summarizes the mechanism of action and evidence based recommended dosages of these agents. Larger controlled studies are still required to formulate explicit guidelines defining usage of these medications.

Acne, Sebocytes, and Androgens

Androgen receptors localized to the basal layer of sebocytes are found in the highest density in human skin. With the onset of puberty, systemic and locally derived testosterone and DHT increase sebum production via AR binding and are also implicated

TABLE 1.

Antiandrogen Therapies: Drugs Used in Clinical Practice*

Therapy	Mechanism of Action	Standard Dose: Acne[25,27]	Standard Dose: Hirsutism[32]	Standard Dose: FPHL[33]
Spironolactone	Androgen Receptor Blocker	25-200mg/d	50-200 mg/d[34]	Not Available in United States
Cyproterone Acetate (CPA) Not Available in United States	-Androgen Receptor Blocker -Inhibits Adrenal Androgen Synthesis	50-100mg/d** on days 5-15 of menstrual cycle or as progestin component of COC: 2mg CPA + 35 µg ethinyl estradiol	50-100mg/d** on days 5-15 of menstrual cycle or as progestin component of COC: 2mg CPA + 35 µg ethinyl estradiol[35,36]	25-50mg/d on days 1-10 of menstrual cycle or as progestin component of COC: 2 mg CPA+ 35 µg ethinyl estradiol
Flutamide/ Bicalutamide	Androgen Receptor Blocker	250-500 mg/d[37]	62.5-500 mg/d[38]. Low dose Bicalutamide 25mg/d also effective.[39]	62.5-250 mg/d[40]
Combined Oral Contraceptives (COC)	-Inhibits LH dependent ovarian androgen production -Increased hepatic synthesis of SHBG to decrease free testosterone	Depends on pill	Depends on pill	Not Used
Finasteride/ Dutasteride	5 α-Reductase Inhibitor	Not Used	5mg daily No clinical data for dutasteride[41]	0.2-5.0 mg/d of finasteride 0.25-0.5 mg/d of dutasteride[42]

*These doses represent effective ranges that vary between disease states.

in follicular hyperkeratinization.[18] Acne formation occurs at the time of rising levels of DHEA-S, which was found to correlate with acne severity in prepubertal girls.[19] Both 5α reductase type I and 17B HSD types 3 and 5 were reported in sebaceous glands from facial areas prone to acne as compared to non acne prone areas, which suggests that local androgen biosynthesis contributes to acne development in those areas.[20] However, though androgens are associated with the evolution of acne, androgen levels are not directly correlated with acne severity.[21] The exact mechanism by which androgens regulate sebocyte activity is still unknown.[8] It has been proposed that AR binding to macrophages and neutrophills enhances the inflammatory milieu necessary for acne formation.[22] Alternatively, IGF-1, one of the androgen receptor target genes, was shown to induce STREBP-1 expression and lipogenesis in sebocytes.[23] Like DHEA-S, IGF-1 is increased during puberty and controls androgen activity in the skin via phosphorylation of the AR corepressor, FOXO1, which then releases its inhibition on AR translocation.[24] Accordingly, patients with Laron syndrome, an inherited IGF-1 deficiency, do not develop acne or hirsutism unless sufficient replacement therapy is initiated. High glycemic load and dairy products increase the expression of IGF-1 and may partially explain the clinical association between diet and acne.[23]

Hormonal therapy for acne is not typically first-line but is indicated in women who desire contraception, those with clinical hyperandrogenism or proven ovarian/adrenal hyperandrogenism, and those who fail to be controlled on repeated isotretinoin courses. Hormonal therapy seems to have greatest efficacy on acne tarda in women and sexually active teens with premenstrual flares[25] and is effective even in the absence of hyperandrogenism. It is rarely used as a monotherapy as current guidelines recommend the use of combination therapy with an oral antibiotic, topical retinoid or benzoyl peroxide to target as many factors of acne pathogenesis as possible.[26] Of all available options, combined oral contraceptives (COC) and spironolactone are the most widely used hormonal agents.[27] A recent Cochrane review of the effectiveness of combined oral contraceptive (COC) therapy for acne found all formulations equally effective in reducing inflammatory and noninflammatory acne lesions. Due to the structural similarity between androgens and progestins, certain progestins have pro-androgenic activity that, overall, is still outweighed by the countering estrogen. However, the use of newer fourth generation progestins, drospirenone and cyproterone acetate (not available in the United States) is clinically recommended as they are not derived from testosterone and function as full androgen receptor antagonists. Nonoral COC's have not been studied and only three COC's are FDA approved for the treatment of acne.[28,29] Spironolactone has shown improvement in 50-100% of treated women at doses of 100-200mg/d.[30] However, doses as low as 25mg once or twice daily have been cited as effective based on clinical experience with the advantage of less toxicity.[27] Targeted enzyme therapy utilizing selective type I 5a reductase inhibitors has not shown significant improvements in acne in both clinical and in vitro studies.[31] This suggests that DHT in particular may not be the primary androgen involved in acne formation.

Hirsutism

Hirsutism is the excessive growth in females of sexual hair in a male pattern distribution.[14] The role of androgens in disease pathogenesis is unequivocal as sexual hair growth is entirely mediated by androgens. Local overproduction of androgen and increased sensitivity of the AR are the two accepted theories of disease pathogenesis. However, most women with hirsutism

typically have systemic hyperandrogenism secondary to an adrenal or ovarian endocrinopathy, most commonly PCOS. Pharmacologic treatment of hirsutism with antiandrogen therapy is a commonly prescribed use of these medications. Meta-analysis of five trials of antiandrogen monotherapy for hirsutism showed significant hair reduction compared to placebo.[43] No significant difference was observed between subgroups, making antiandrogen selection primarily based on patient preference and cost. Both antiandrogen and COC monotherapy were found equally effective,[44] but the 2008 Endocrine Society Guidelines recommend COC as first line due to risks of pseudohermaphrodism in male fetuses with antiandrogens alone. Though COC and antiandrogen therapy together was more effective than COC alone, combination regimens should only be initiated after six months of suboptimal treatment with either agent alone. Guidelines recommend against GnRH agonists and flutamide due to toxic side effect profiles. Flutamide has less affinity for the androgen receptor than spironolactone and therefore higher doses are generally required. However, some researchers have reported doses as low as 62.5 mg/d of flutamide to be effective, thus limiting the risk of hepatotoxicity.[38] Topical antiandrogens and insulin lowering drugs are also not recommended due to (inconsistent) data showing limited efficacy. Published guidelines are currently limited by poor quality evidence and larger randomized controlled trials are required for a more authoritative stance on the effectiveness of hormonal therapy for hirsutism.[43]

Androgenetic Alopecia

The hallmark of both male and female pattern baldness is follicular miniaturization with progressive shortening of the anagen phase. This leads to the transformation of terminal hairs into shorter, finer vellus hairs that fail to reach the scalp surface. Histological similarity does not necessarily confer a common etiology and while male pattern hair loss, appropriately referred to as male androgenetic alopecia (MAGA), has clearly been identified as an androgen mediated disease, the role of sex steroids in the female pattern is not well established. In addition, different prevalence rates, peak onset, and most importantly, the pattern of loss, are clinical evidence of their status as distinct entities.[45]

DHT is considered the main mediator of male pattern baldness.[45] Evidence to support the central role of DHT stems from observations that individuals who lack the 5α reductase type II enzyme do not develop androgenetic alopecia,[46] as well as studies showing an increased concentration of DHT in hairs plucked from balding scalps.[47] Both AR expression and cellular levels of 5α reductase type II have been found to be increased in the bald frontoparietal scalp as compared to the occipital scalp, which explains why the occipital scalp is resistant to the effects of androgens.[47] When treated with excess androgen, dermal papilla cells from a balding scalp lose their ability to stimulate keratinocyte proliferation and increase TGFβ secretion, a keratinocyte growth inhibitor. Genetic association studies have also highlighted AR genetic variation in the heritability of this complex, polygenic trait. A particular SNP found in the noncoding, exon 1 region of the AR gene is present in 100% of balding men and CAG and GGC polymorphisms in the amino terminal domain of the AR gene have been implicated with the risk of developing MAGA when shortened. Though neither mutation leads to an altercation in protein expression or function, these findings form the basis of the as yet controversial genetic susceptibility tests for pattern hair loss.[48]

The role of sex steroids in female pattern hair loss (FPHL) is less known and androgen excess is generally not a prerequisite for FPHL.[45] Those with peripheral hyperandrogenism develop a male, not female, pattern of hair loss and there is conflicting results in the literature regarding the efficacy of antiandrogen therapy for women without overt hyperandrogenism.[49] The pattern differences in MAGA and FPHL may be due to the influence of estrogens, which modify androgen metabolism at the hair follicle via inhibition of 5α reductase or conversion of testosterone to weaker androgens.[33,50] Crashing levels of estrogen in the post pregnancy and menopausal states, and the accompanying hair loss, contribute to the suspicion that low levels contribute to FPHL. Topical estrogen therapy has been used outside the USA for the treatment of FPHL[51] but efficacy has not been confirmed.

Finasteride 1mg/d is FDA approved for the treatment of MAGA. Conflicting reports on efficacy has led to the investigation of dutasteride, a dual type I and II 5a reductase inhibitor, which has shown increased potency in inhibiting both isozymes and can decrease serum DHT by more than 90%.[49] Finasteride 1mg/d was found ineffective in postmenopausal women after 12 months of treatment[52] and this study has been used to support the non-androgen nature of FPHL. However, the study did not evaluate premenopausal women and at higher doses and when combined with COC, finasteride has exhibited clinical efficacy.[53] A topical preparation of 0.05% finasteride is being evaluated for both MAGA and FPHL.[54] Spironolactone and cyproterone acetate are the most commonly prescribed antiandrogens for FPHL and have shown clinical efficacy,[49,53] but larger randomized controlled trials are needed to fully assess the therapeutic potential of these agents. Topical spironolactone 2% solution has shown variable success when combined with minoxidil.[33] A novel new topical antiandrogen, fluridil has shown efficacy in both MAGA and FPHL and though used throughout Europe, is currently awaiting FDA approval for use in the United States.

Conclusion

The pilosebaceous unit is not only influenced by androgens, but contributes to and regulates cutaneous androgen production. Increased local concentrations are thought to mediate the development of acne, hirsutism and androgenetic alopecia, which explains the well-established role of antiandrogen therapy in those disease states. Continued investigation into peripheral steroidogenesis will provide more targeted therapy for the treatment of androgen dependent dermatoses.

Disclosure

The authors have no relevant conflicts to disclose.

Aimee Krausz BA[a] and Adam J. Friedman MD[a,b]

[a]Department of Medicine (Division of Dermatology) and [b]Department of Physiology and Biophysics, Albert Einstein College of Medicine, Bronx, NY

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