Hirsutism and the Variable Response of the Pilosebaceous Unit to Androgen

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The pilosebaceous unit (PSU) response to androgen is variable. Certain population of PSU respond to androgen in a distinctive pattern that results in sexual hair development in some, sebaceous gland development in others. Furthermore, androgen excess is variably manifest in women as hirsutism, acne vulgaris, seborrhea, or pattern alopecia. Although sebaceous cells act as intracrine cells, activating pro-hormones to potent androgens that act within the sebocyte, hair follicle metabolism predominantly inactivates testosterone. Androgen action in the sexual hair follicle appears to be mediated by the dermal papilla and possibly, by inducing expression of a specific keratin, hHa7, in the hair medulla. The data do not clearly support a relationship between idiopathic hirsutism, the hirsutism that occurs in the absence of androgen excess, and variations in androgen mechanism of action. Androgens are prominent among the hormones that modulate the biological mechanism regulating the hair cycle. However, the basis for the variable pattern of PSU response to androgen is unclear, as is the basis for the variable development of hirsutism in response to androgen excess and the incomplete reversal of hirsutism by anti-androgen treatment. Improved treatment of hirsutism awaits improved understanding of the nature of the interaction between androgens and other determinants of hair follicle biology.

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The pilosebaceous unit (PSU) is known to not only be a target for androgen and for other hormones, it is additionally a source of hormones (Deplewski and Rosenfield, 2000; Alonso and Rosenfield, 2003). This information is here updated with the intent to understand how hormones may interact with the local PSU factors that regulate hair morphogenesis and cycling to determine the variable response of the PSU to androgen.

The Clinical Enigma

Particular populations of prepubertal vellus follicles in humans undergo two distinctly different patterns of development in response to the normal increase in androgen levels at puberty: one population develops into sexual hair follicles, whereas another develops into sebaceous glands. Sexual hair development occurs in a distinctive pattern that is related to the plasma concentration of androgens. Pubic and axillary hair develop at plasma androgen levels in the normal adult female range (testosterone about 20–70 ng per dL), more sexual hair appears as testosterone levels rise above the normal adult female range, and full beard and mustache growth typically occur in response to testosterone levels in the normal adult male range (about 310–1100 ng per dL). This suggests that beard PSUs are about one-tenth as sensitive as axillary hairs to induction of terminal hair growth by androgens. This contrasts with sebum formation normally being about three-quarters as great at female levels as at male levels of androgen. Noteworthy is that some degree of variability in the PSUs response to androgen is apparent at normal androgen levels. Some women develop excessive sexual hair in a male pattern (hirsutism) at normal female androgen levels; this "idiopathic hirsutism" accounts for about half of mild hirsutism. Acne vulgaris or seborrhea may also occur at normal androgen levels, indicating a similarly variable response of the sebaceous follicle type of PSU to androgen.

Another manifestation of the variability in PSU response to androgen is pattern alopecia. In this situation, the more midline scalp hairs anterior to the vertex that have grown independently of androgens from birth gradually begin to regress so as to become vellus follicles in genetically susceptible individuals; the inheritance pattern is polygenic (Nyholt *et al*, 2003; Price, 2003). Interestingly, scalp hair growth is slower at the crown and that of boys is faster than that of girls in the neonatal period (Solomon and Esterly, 1970). Pattern hair loss ("androgenetic alopecia") is most prominent in men and typically begins in a fronto-temporal pattern. Adult male plasma androgen levels are a prerequisite; it begins after puberty and increases with age. Female pattern hair loss ordinarily begins in a fronto-parietal pattern and is more diffuse. The onset is typically in the third or fifth decade, and it is androgen independent more often than not (Olsen, 2001; Vexiau *et al*, 2002; Price, 2003).

In response to elevated levels of androgen, another aspect of the variable PSU response to androgen becomes

Abbreviations: IGF-I, insulin-like growth factor-I; PSU, pilosebaceous unit; PTHrP, parathyroid hormone-related peptide

apparent: hirsutism, acne vulgaris, and pattern alopecia are variably expressed manifestations of androgen excess. At modest elevations of androgen (up to about 2-fold) some women will not develop hirsutism. Some of these cases have no skin manifestations whatsoever ("cryptic hyperandrogenemia"); others have seborrhea, acne, or pattern alopecia instead (Orfanos *et al*, 2000). Only as testosterone levels reach the mid-pubertal male range (over about 5-fold elevated), will most women have hirsutism; however, the degree will vary widely, from modest to severe.

These disparities in the response of PSU to androgen indicate interactions between androgen levels and intrinsic properties of PSU that can be characterized as differences in genetic programming or in sensitivity to androgen. What might be the basis for these variable PSU responses to androgen? This requires understanding how androgens interact with the PSU and local factors regulating hair biology.

The Endocrinology and Intracrinology of the PSU

Androgens are primarily secreted by the gonads and adrenal cortices. In adult women, these two sets of glands contribute about equally to androgen production; however, half of androgens in the female are secreted as pro-hormones (Rosenfield, 1972). The skin is a major site of the metabolic activation of these hormone precursors (Labrie *et al*, 2000; Chen *et al*, 2002).

Within skin, steroid metabolism occurs in a manner characteristic of the appendage in a manner suggestive that some of these differences may account for variations in the responsiveness of these target glands to androgen. The sebaceous glands and sweat glands account for over 75% of steroid activation. The sebaceous glands possess the type 1 3β-hydroxysteroid dehydrogenase, type 5 17β-hydroxysteroid dehydrogenase, and type 1 5α reductase activities that, respectively, allow them to convert dehydroepiandrosterone (DHEA) sequentially to androstenedione, testosterone, and dihydrotestosterone (DHT). DHT is the most potent androgen receptor ligand. These enzymes have recently been localized to the sebocytes themselves (Thiboutot *et al*, 2003). Sebocytes express only a trace amount of cytochrome P450c17, a key enzyme that would give them the capacity to form DHEA from cholesterol as do the adrenal glands and gonads. Thus, sebaceous cells act as intracrine cells, that is, they activate pro-hormones to potent androgens that act within the cell that forms them (Labrie *et al*, 2000).

The enzymatic apparatus of hair epithelium, in contrast, predominantly functions in the reverse mode, that is, to inactivate androgen (Glickman and Rosenfield, 1984; Maudelonde *et al*, 1986). Nevertheless, it expresses some 5α-reductase and androgen receptor activity, less-so in the frontal and occipital scalp hair follicles of women than men, which may be one factor protecting women from androgenetic alopecia (Price, 2003).

But the dermal papillae of hair follicles appear to play an important paracrine role in PSU development by supplying potent androgens to the closely apposed germinative matrix epithelial cells (Ando *et al*, 1999). The expression of mRNA for the type 3 17β-hydroxysteroid dehydrogenase that most efficiently forms testosterone from androstenedione has been detected. Dermal papillae also express relatively high levels of the 5α-reductase activity that forms DHT from testosterone. Those of beard possess the most potent type of 5α-reductase (type 2) activity. Axillary dermal papillae express type 2 5α-reductase mRNA in greater amounts than those of beard, although this finding is not entirely consistent with reported enzyme activity data.

A promising clue to the potential mechanism by which androgen may specifically stimulate sex hair growth has recently emerged. The promoter of keratin hHa7, a keratin specifically expressed in the medulla of sex hairs, contains an androgen response element that is transactivatable by androgen (Jave-Suarez *et al*, 2004).

Is idiopathic hirsutism related to variations in androgen mechanism of action? Most data does not provide convincing evidence for this possibility. No excessive DHT formation has been detected in plucked sexual hairs. Although skin of these patients has increased 5α-reductase activity, this may well be attributable to the sebaceous gland hyperplasia that accompanies androgen excess. No abnormality of androgen receptor binding has been detected in genital skin fibroblasts, and skewed X inactivation—with shorter CAG repeats being expressed significantly more—is doubtful as two of three studies have been negative.

Some idiopathic hirsutism patients have sexual hairs that are larger than normal (Glickman and Rosenfield, 1984). Sexual hair development, particularly the larger hairs of the beard, can be reversed by about 50% at most by combination treatment with anti-androgen and gonadotropin suppression (Giltay and Gooren, 2000; Farquhar *et al*, 2003; Van der Spuy and le Roux, 2003).

Dermal papilla cells seem to be the primary target of androgen in hair. Androgen stimulates the growth of hair outer root sheet cells only in the presence of co-cultured dermal papilla cells (Itami *et al*, 1995). Insulin-like growth factor-I (IGF-I) appears to mediate this hair epithelial cell growth in response to androgen. These observations suggest that variations in androgen action depend upon the interaction of androgens with other biological factors. What is known about this?

Hormonal Interactions with Hair Morphogenesis and Cycling

All available evidence suggests that hair follicle morphogenesis is hormone independent. Males and females are born with a similar number of PSU. It is their differentiation pattern that is determined by androgen, not their number. IGF-I receptor deletion mutants have small sparse hair follicles, but this appears to be a consequence of the general blighting of growth of the skin, indeed the body, as a whole. The only point in PSU morphogenesis at which any hormonal factor has been specifically incriminated is in the transition from the hair peg stage, the branch point at which the hair follicle lineage and the sebaceous gland lineage diverge. Along with Indian hedgehog (Niemann *et al*, 2003) and tumor necrosis factor receptor-associated factor 6, parathyroid hormone-related peptide (PTHrP) is a determinant

Table I. Hormonal factors in hair growth

Steroid hormones
Androgen
Glucocorticoid
Estrogen
Peptide hormones
Growth hormone/insulin-like growth factor-I
Parathyroid hormone related peptide
Prolactin
Thyroid hormone
Nuclear receptors
Vitamin D receptor
Retinoid X receptor

of the sebaceous gland lineage. Prenatal over-expression of PTHrP has a sexually dimorphic, spatially limited effect on hair growth: ventral hairs are sparse, particularly in females. The sexual dimorphism appears to have an indirect basis, however (Abdalkhani *et al*, 2002). The apparent sequence of events is that androgens normally suppress mammary gland development, so that males have too little mammary epithelium to express sufficient PTHrP to promote mammary development at the expense of hair follicle development. Only females have sufficient mammary gland development to express enough PTHrP to suppress ventral hair growth.

It is the hair follicle cycle that is hormone dependent. Multiple hormonal factors interact with various growth factors, transcription factors, and transcriptional co-regulators expressed by the hair follicle, such as fibroblast growth factor 5, deletion of which underlies the angora mouse mutation by prolonging anagen. Hormonal factors known to affect the hair cycle are shown in Table I.

Notably, of these, only androgen and the growth hormone/IGF system are known to stimulate hair growth. Growth hormone potentiates the effect of androgen on sexual hair growth; about 5-fold more testosterone is required to induce axillary hair in growth hormone-deficient than in growth hormone-sufficient hypogonadal boys. IGF-I is produced by the dermal papilla cells, but not by hair epithelial cells, and the IGF-I receptor is expressed by hair matrix epithelium as well as by dermal papilla cells, thus constituting an autocrine–paracrine system for hair growth. IGF-I (or high-dose insulin) is necessary for hair follicle growth *in vitro*.

Most other hormonal factors promote catagen entry. Although glucocorticoids promote catagen (Paus *et al*, 1994), paradoxically glucocorticoid excess causes hypertrichosis. Most evidence indicates that estrogen promotes catagen (Conrad and Paus, 2004; Ohnemus *et al*, 2004). Thus, estrogen may be responsible for the arrest of hair growth late in pregnancy (Solomon and Esterly, 1970), which sets the stage for telogen effluvium upon the withdrawal of pregnancy hormones. On the other hand, the higher expression of aromatase in the scalp hairs of women than men, particularly on the occiput, suggests that local estrogen formation from testosterone may play a role in protecting them from alopecia (Price, 2003).

The PTHrP/receptor system constitutes a paracrine system within the hair follicle. Hair epithelium expresses PTHrP, whereas the dermal papilla and dermal sheath express its receptor (Cho *et al*, 2003; Thomson *et al*, 2003). Postnatally, PTHrP or parathyroid hormone, which interacts with the same receptor, promotes catagen, and PTHrP over-expression partially corrects the long hair of angora mice. The PTHrP effect is independent of serum calcium levels and is being explored as a way of protecting hair follicles from chemotherapy-induced alopecia (Peters *et al*, 2001).

An autocrine–paracrine role for prolactin within the hair follicle is suggested by the fact that prolactin and its receptor have been localized to different portions of the hair follicle epithelium (Foitzik *et al*, 2003). Although prolactin administration induces premature entry into catagen, clinically prolactin excess is associated with hirsutism, probably because of stimulation of hyperandrogenism by prolactin excess.

Thyroid hormone appears to regulate the frequency of the hair cycle: hypothyroidism leads to decreased frequency of anagen, whereas hyperthyroidism leads to thin hairs. Triiodothyronine therapy improves hair growth of the hairless (Hr) mouse, which has congenital total atrichia, although the thyroid hormone mechanism of action is unlikely to involve the Hr gene product (Engelhard and Christiano, 2004).

Notably, the vitamin D-retinoid X receptor system is necessary for postnatal cycling of the hair follicle. This occurs by interaction with the Hr transcription factor (Hsieh *et al*, 2003). These effects are ligand independent. Consequently, individuals born with vitamin D receptor deletions suffer from postnatal alopecia that cannot be corrected by calcium administration.

Summary

The basis for the variable pattern of PSU response to androgen is unclear, as is the basis for the variable development of hirsutism in response to androgen excess and the incomplete reversal of hirsutism by anti-androgen treatment. Improved treatment of hirsutism awaits improved understanding of the nature of the interaction between androgens and other determinants of hair follicle developmental biology.

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References

Abdalkhani A, Sellers R, Gent J, *et al*: Nipple connective tissue and its development: Insights from the K14-PTHrP mouse. Mech Dev 115:63–77, 2002

Alonso LC, Rosenfield RL: Molecular genetic and endocrine mechanisms of hair growth. Horm Res 60:1–13, 2003

Ando Y, Yamaguchi Y, Hamada K, Yoshikawa K, Itami S: Expression of mRNA for androgen receptor, 5alpha-reductase and 17beta-hydroxysteroid dehydrogenase in human dermal papilla cells. Br J Dermatol 141:840–845, 1999

Chen W, Thiboutot D, Zouboulis CC: Cutaneous androgen metabolism: Basic research and clinical perspectives. J Invest Dermatol 119:992–1007, 2002

Cho YM, Woodard GL, Dunbar M, Gocken T, Jimenez JA, Foley J: Hair-cycle-dependent expression of parathyroid hormone-related protein and its type I receptor: Evidence for regulation at the anagen to catagen transition. J Invest Dermatol 120:715–727, 2003

Conrad F, Paus R: Estrogens and the hair follicle. J Deutsch Dermat Ges 2:412–423, 2004

Deplewski D, Rosenfield RL: Role of hormones in pilosebaceous unit development. Endocr Rev 21:363–392, 2000

Engelhard A, Christiano AM: The hairless promoter is differentially regulated by thyroid hormone in keratinocytes and neuroblastoma cells. Exp Dermatol 13:257–264, 2004

Farquhar C, Lee O, Toomath R, Jepson R: Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Cochrane Database Syst Rev CD000194: 2003

Foitzik K, Krause K, Nixon AJ, Ford CA, Ohnemus U, Pearson AJ, Paus R: Prolactin and its receptor are expressed in murine hair follicle epithelium, show hair cycle-dependent expression, and induce catagen. Am J Pathol 162:1611–1621, 2003

Giltay EJ, Gooren LJ: Effects of sex steroid deprivation/administration on hair growth and skin sebum production in transsexual males and females. J Clin Endocrinol Metab 85:2913–2921, 2000

Glickman SP, Rosenfield RL: Androgen metabolism by isolated hairs from women with idiopathic hirsutism is usually normal. J Invest Dermatol 82:62–66, 1984

Hsieh JC, Sisk JM, Jurutka PW, Haussler CA, Slater SA, Haussler MR, Thompson CC: Physical and functional interaction between the vitamin D receptor and hairless corepressor, two proteins required for hair cycling. J Biol Chem 278:38665–38674, 2003

Itami S, Kurata S, Takayasu S: Androgen induction of follicular epithelial cell growth is mediated via insulin-like growth factor-I from dermal papilla cells. Biochem Biophys Res Commun 212:988–994, 1995

Jave-Suarez LF, Langbein L, Winter H, Praetzel S, Rogers MA, Schweizer J: Androgen regulation of the human hair follicle: The type I hair keratin hHa7 is a direct target gene in trichocytes. J Invest Dermatol 122: 555–564, 2004

Labrie F, Luu-The V, Labrie C, Pelletier G, El-Alfy M: Intracrinology and the skin. Horm Res 54:218–229, 2000

Maudelonde T, Rosenfield RL, Shulers CF, Schwartz SA: Studies of androgen metabolism and action in cultured hair and skin cells. J Steroid Biochem 24:1053–1060, 1986

Niemann C, Unden AB, Lyle S, Zouboulis Ch C, Toftgard R, Watt FM: Indian hedgehog and beta-catenin signaling: Role in the sebaceous lineage of normal and neoplastic mammalian epidermis. Proc Natl Acad Sci USA 100 (Suppl 1):11873–11880, 2003

Nyholt DR, Gillespie NA, Heath AC, Martin NG: Genetic basis of male pattern baldness. J Invest Dermatol 121:1561–1564, 2003

Ohnemus U, Unalan M, Handjiski B, Paus R: Topical estrogen accelerates hair regrowth in mice after chemotherapy-induced alopecia by favoring the dystrophic catagen response pathway to damage. J Invest Dermatol 122:7–13, 2004

Olsen EA: Female pattern hair loss. J Am Acad Dermatol 45:S70–S80, 2001

Orfanos CE, Adler YD, Zouboulis CC: The SAHA syndrome. Horm Res 54: 251–258, 2000

Paus R, Handjiski B, Czarnetzki BM, Eichmuller S: A murine model for inducing and manipulating hair follicle regression (catagen): Effects of dexamethasone and cyclosporin A. J Invest Dermatol 103:143–147, 1994

Peters EM, Foitzik K, Paus R, Ray S, Holick MF: A new strategy for modulating chemotherapy-induced alopecia, using PTH/PTHrP receptor agonist and antagonist. J Invest Dermatol 117:173–178, 2001

Price VH: Androgenetic alopecia in women. J Investig Dermatol Symp Proc 8: 24–27, 2003

Rosenfield RL: Role of androgens in growth and development of the fetus, child, and adolescent. Adv Pediatr 19:171–213, 1972

Solomon LM, Esterly NB: Neonatal dermatology. I. The newborn skin. J Pediatr 77:888–894, 1970

Thiboutot D, Jabara S, McAllister JM, Sivarajah A, Gilliland K, Cong Z, Clawson G: Human skin is a steroidogenic tissue: Steroidogenic enzymes and cofactors are expressed in epidermis, normal sebocytes, and an immortalized sebocyte cell line (SEB-1). J Invest Dermatol 120:905–914, 2003

Thomson M, McCarroll J, Bond J, Gordon-Thomson CEDW, Moore GP: Parathyroid hormone-related peptide modulates signal pathways in skin and hair follicle cells. Exp Dermatol 12:389–395, 2003

Van der Spuy ZM, le Roux PA: Cyproterone acetate for hirsutism. Cochrane Database Syst Rev CD001125: 2003

Vexiau P, Chaspoux C, Boudou P, Fiet J, Jouanique C, Hardy N, Reygagne P: Effects of minoxidil 2% vs cyproterone acetate treatment on female androgenetic alopecia: A controlled, 12-month randomized trial. Br J Dermatol 146:992–999, 2002