Male androgenetic alopecia

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Summary

Androgenetic alopecia (AGA) is the most common type of hair loss in men. The relative strong concordance of the degree of baldness in fathers and sons is not consistent with a smiple Mendelian trait and a polygenic basis is considered to be most likely. So far the predisposing genes for AGA are unknown and we do not understand the molecular steps involved in androgen-dependent beard growth versus androgen-dependent hair loss, but AGA can be defined as a DHT-dependent process with continuous miniaturization of sensitive hair follicles. The type 2 5aR plays a central role by the intrafollicular conversion of T to DHT. Due to the inceasing knowledge in this field, this article shall privide an critical overwiew of recent discoveries.

Introduction

Androgenetic alopecia (AGA) is the most common type of hair loss in men. This continuous process results in a type of alopecia that follows a definite pattern in those individuals who are genetically predisposed. This androgen-dependent condition is often referred to as male pattern, or common, baldness. The prevalence of progressive AGA approaches 50% of Caucasian men beyond the age of 40 years, whereas in Asian, native American and African–American men the prevalence is lower and AGA is less severe. All the hairs in an affected area may be involved in the miniaturization process and over the time the region may be covered with fine, hardly visible vellus hairs. Along with hair miniaturization the production of pigment ceases. There is still a controversy as to whether the total number of hair follicles decreases during AGA. However, it can be assumed that some hairs in AGA are definitely lost, but the majority of hair shafts are still present as tiny vellus hairs. The pathogenesis of AGA is not completely understood, but rather recent experimental and clinical advances enable us to explain some steps leading to androgenetic hair loss. Therefore, this review provides a critical account of the current understanding of the etiopathology of AGA in men.

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Inheritance

The relative strong concordance of the degree of baldness in fathers and sons is not consistent with a simple Mendelian trait and a polygenic basis is considered to be most likely.[1,2] The predisposing genes are still unknown. The genes for type 1 and type 2 5α-reductase (5α-R) and steroid sulphatase[3,4] are not associated with the inheritance of AGA.[1,5] It has been postulated that polycystic ovaries (PCO) in females and early onset AGA in brothers of those PCO-affected women are associated with one allele of the steroid metabolism gene CYP17 which affects androgen production or action.[6,7] Another suceptibility gene for PCO has been linked to a polymorphism of the insulin gene.[8] In man, the number of CAG repeats is polymorphic and expansion of CAG repeats in the androgen receptor (AR) has clinical implications for human disease. Shorter CAG-repeat lengths may be associated with the development of androgen-mediated skin disorders in men and women.[9] However, the androgen receptor gene is located on the X chromosome and does not explain father-to-son inheritance. On the other hand, we recently described individuals suffering from adrenoleukodystrophy, an X-chromosomal recessive trait; although affected men tend to have low serum testosterone concentrations,

one of the clinical hallmarks is a severe AGA-like hair loss with early onset. We therefore hypothesized that one of the AGA-predisposing genes might be the X-linked gene for adrenoleukodystrophy.[10]

Animal models

Several animal species have been reported to develop hair loss resembling human androgenetic alopecia, including bears, lions and non-human primates. Androgen-dependent hair growth has also been described in the red deer. However, a well-studied non-human baldness model is the stump-tailed macaque which is a protected species. These macaques have been used to assess the efficacy of several compounds to treat androgenetic hair loss such as minoxidil, systemic 5α-reductase inhibitors, and topical androgen receptor blockers.[11–14] In the larger species, the animals are outbred, and the high costs of maintenance makes them of little practical use as research models. Rodent models can be used in several ways for testing modes of therapy or disease prevention. In male Spraque–Dawley rats it has been shown that the hair growth of the dorsal coat appears to be androgen-dependent. Castration of male rats resulted in an accelerated entry into anagen III, whereas supplementation with testosterone inhibited this process.[15] The hair shafts of castrated rats appeared to be thicker and hair loss was not observed. At present only one strain of mice, the androchronogenetic mouse, has been described that displays an AGA-like hair loss. This hair loss can be aggravated by infusion of testosterone or DHT and is on the other hand treatable with minoxidil or cyproterone acetate.[17,18] So far, however, no further studies have been performed by use of this model. Another approach has been to transplant human hair follicles from androgen-dependent sites of the scalp (frontal hair) onto testosterone-conditioned nude mice and to measure the hair cycles of these hair follicles and to assess the effect of several drugs on growth characteristics of these hairs.[16]

Pathogenesis

More than 50 years ago Hamilton observed that men who were castrated did not develop AGA.[19] Therefore, it was concluded that the growth of hair follicles is in some areas androgen-dependent (Table 1). At present it is not known how androgens exert their paradoxic effect on the growth of hair follicles at different body sites, and which genes are involved. However, Hamilton showed that AGA can be triggerd in castrated men by injecting testosterone.

Table 1 Different effects of androgens on hair growth.

Androgen-insensitive hair follicles: These hair follicles grow without the influence of androgens (occipital scalp hair follicles and of the eyelids).
Androgen-dependent hair follicles: These hair follicles enlarge in response to androgens to grow longer and thicker hairs (e.g. the beard).
Androgen-sensitive hair follicles: These hair follicles display a shortening of the anagen phase and miniaturization of the hair follicle, which results in the formation of progressively thinner and shorter hair (frontal scalp hair in AGA).

Minimal to no beard growth or AGA is seen in pseudohermaphrodites who lack 5α-reductase, indicating that DHT, the 5α-reduced metabolite of testosterone is the principal mediator of androgen-dependent hair loss. Interestingly, 5α-reduced metabolites of testosterone are increased in balding areas of the human scalp as well as in the scalp of the stump-tailed macaques. It is not yet clear whether DHT is derived from the local metabolism or from the circulation, but it can be assumed that under the influence of DHT hair loss is characterized by a shortening of the anagen phase and miniaturization of the hair follicle, which results in thinner and shorter hair. There is considerable support for the idea that hair follicle size is determined by the size of its dermal papilla. Van Scott[20] demonstrated a constant geometric correlation between the proportions of the human hair follicle, the dermal papilla and the hair bulb matrix. They concluded that the size of the dermal papilla ultimately dictates the size of the growing hair. Hence, in AGA some dermal papilla cells will get lost. The most likely mechanism is by apoptosis, but cell displacement might be an additional explanation.

Androgen metabolism and hair growth

As stated above, androgens are necessary to develop AGA and the androgen metabolism within target cells is of crucial importance. The literature, however, on normal and pathologic androgen metabolism (AM) is vast, and contradictory studies are a source of additional confusion. Here, some pivotal aspects of AM which are important for hair growth are reviewed.

Androgen metabolism can be divided into glandular and extraglandular production, transport, target cell metabolism and cellular response. The synthesis of androgens is complex because it occurs in several organs, each of which has its own pecularities. The androgen metabolism of adrenals and gonads and the influence of the pituitary gland are beyond the scope of this review and are described in detail elsewhere.[21]

Androgen synthesis begins with cholesterol which is converted to pregnenolone. Following α-hydroxylation at the C17-position, the action of the enzyme C17-20 lyase cleaves distal carbon moieties, leaving a C-19 carbon steroid with a C-17 ketone in the distal ring. These '17-ketosteroids' make up a group of relatively weak androgens, such as dehydroepiandrosterone (DHEA), defined by their relatively low affinity for the androgen receptor. Approximately 75% of DHEA and 95% of dehydroepiandrosterone sulphate (DHEA-S) is derived from the adrenal gland. These weak androgens can be enzymatically converted to more potent androgens such as testosterone, which is the major circulating androgen. In the hair follicle the principial pathways involved in the conversion of weak to more potent androgens are through activity of the enzymes 3β-hydroxysteroid dehydrogenase/$\Delta^{5\rightarrow4}$-isomerase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD). In most target organs testosterone can be further metabolized to DHT via the action of 5α-reductase (Fig. 1). The affinity of DHT to the androgen receptor is approximately fivefold higher than that of testosterone. Potent androgens such as testosterone or DHT can be removed by conversion to weaker androgens, or they can be metabolized via the aromatase to oestrogens, or they can be glucuronidated to form androgen conjugates that are more rapidly cleared from the circulation.

Some target tissues show enhanced AM and androgen sensitivity.[21] Circulating DHEA-S may be more rapidly metabolized to DHEA via steroid sulphatase. In turn DHEA may be more rapidly converted to androstenedione if increased 3β-HSD activity is present. Androstenedione may be converted to testosterone if 17β-HSD activity is present. If target cells convert weak androgens at an accelerated pace, then there will be enhanced conversion of testosterone to DHT. Another reason for increased sensitivity of a target to androgens is believed to involve an increase in the number of androgen receptors.

Only a small fraction of androgens exist as free steroids in the circulation, with an equilibrium between free androgen hormone and protein-bound androgens. The most important protein for androgen binding is sex-hormone binding globulin (SHBG). Approximately 70% of testosterone is bound to SHBG, 19% to albumin and only the remainder is unbound. Whether the bound fractions are still metabolically active is a matter of controversy, but binding of androgens to SHBG is an important factor in AM because it acts somehow as a 'sink' for circulating testosterone.

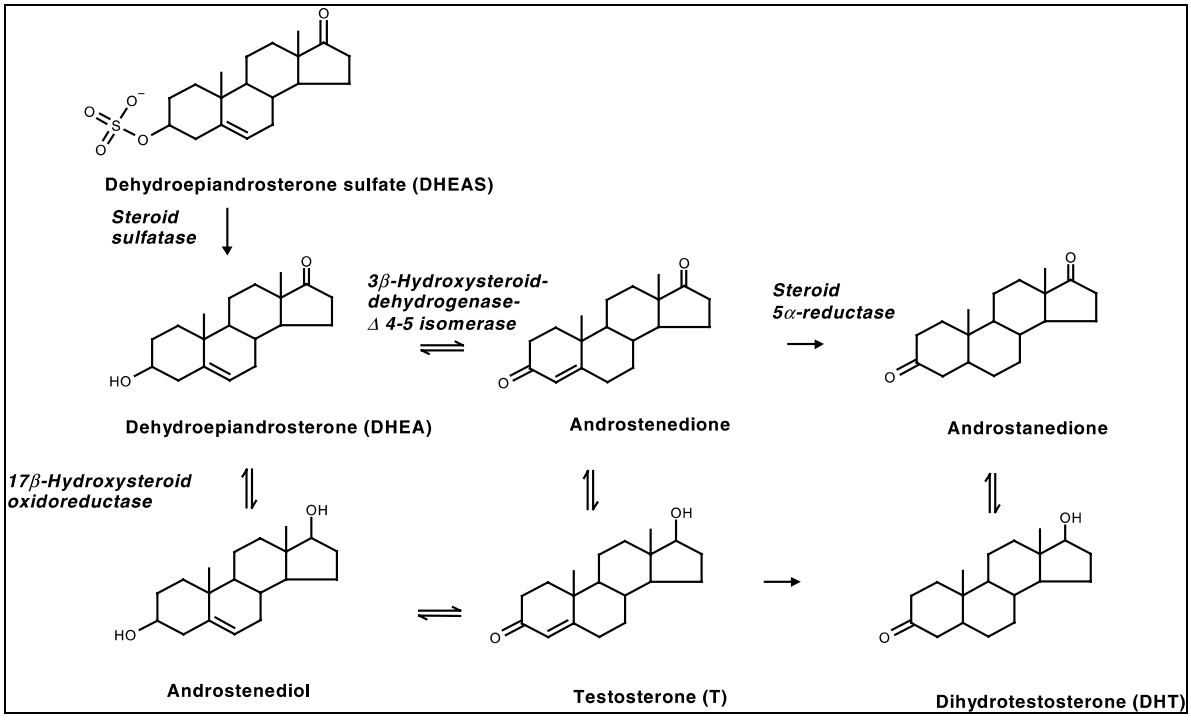

Figure 1 Androgen metabolic pathways.

Like all steroid hormones, androgens exert their effects by binding to an intracellular receptor, the androgen receptor. Binding of androgens to their androgen receptor leads to conformational change of the AR-androgen complex (ARAC) which is then transported into the nucleus where it can bind to regions of DNA that have distinctive binding sites known as androgen-responsive elements (ARE). A wide variety of proteins have this ARE encoded in their DNA. In this way androgens are able to modulate the transcription of various genes, that may be activated or suppressed.

In summary, the AM is highly complex and can be tuned at various points, e.g. the amount of weak androgens present for conversion to more potent androgens, the repertoire of metabolizing enzymes present in target cells, the ratio of conversion and backconversion, the concentration of SHBG in the serum, the affinity of androgens to the androgen receptor, etc. Furthermore, most target organs differ in their repertoire of metabolizing enzymes and this repertoire is different in men and women. Moreover, many metabolizing enzymes have isoenzymes with different tissue distribution, substrate affinity and enzymatic kinetics.

The principal elements of androgen metabolism

Androgen-dependent processes are not the result of the summation of the activity of individual metabolites, but are solely due to the binding of DHT and translocation of the receptor to the nucleus. This concept has been discussed for the development of benign prostate hyperplasia[22] and is most likely valid for AGA as well. Therefore DHT-dependent cell functions will only be initiated or amplified if:

- enough weak androgens are present for conversion;
- more potent androgens are formed via the action of 5α-reductase;
- the enzymatic activity of androgen inactivating enzymes is low, e.g. aromatase;
- conversion of weaker steroids to DHT takes places by, e.g. 3β-HSD or oxidative 3α-HSD;
- functionally active androgen receptors are present in high numbers.

That this simplified concept is valid is nicely illustrated by mutations of androgen metabolizing genes, where often a lack of potent androgens leads to disturbed masculinization or to intersexuality.

Lessons to be learned from steroidogenic enzyme mutations

The synthesis and regulation of steroidogenic enzymes requires an orchestrated expression of biosynthetic enzymes in various tissues. Deficiency of one of these enzymes results in disturbed synthesis of one or more classes of hormones. Here, some genetic diseases affecting male sexual development and hair growth and the potential localization of these enzymes with the hair follicle will be described and their role during the pathogenesis of AGA will be briefly discussed.

Steroid sulphatase

The skin is able to synthesize active androgens, such as DHT, from the systemic precursor DHEA-S. The first step in this pathway is the desulphatation of DHEA-S by the enzyme steroid sulfatase. Because DHEA is further metabolized to androstendione, testosterone, and in special target tissues eventually to DHT, steroid sulfatase is an important enzyme for the conversion of the weak adrenal androgens to more potent androgens in the periphery. DHEA-S is believed to maintain axillary hair and is thought to be involved in the pathogenesis of hirsutism in women.[23] However, in women an excess of DHEA-S or its steroid sulfatase metabolite is believed to be involved in several androgen-dependent processes such as acne and AGA. Remarkably, DHEA-S and DHEA plasma levels seem to correlate with balding in young men indicating that steroid sulfatase may play a role in the pathogenesis of AGA.[24] Today the conversion of DHEA-S to DHEA by human hair follicles is well documented,[25] and recently we were able to show that steroid sulphatase is located mainly within the dermal papilla (Fig. 2).[26]

3β-hydroxysteroid dehydrogenase/$\Delta^{5\rightarrow4}$-isomerase

The 3β-HSD isoenzymes catalyse an obligatory step in the biosynthesis of androgens, oestrogens, mineralocorticoids and glucocorticoids. These steroids play a crucial role in the differentiation, development, growth, and physiological function of most human tissues. The enzyme is expressed in the adrenal cortex and in steroidogenic cells of the gonads, as well as in many other tissues such as the liver and kidney. The two 3β-HSD isoforms are expressed in a tissue-specific manner involving separate mechanisms of regulation. The structures of several cDNAs encoding 3β-HSD isoenzymes have been characterized in humans and

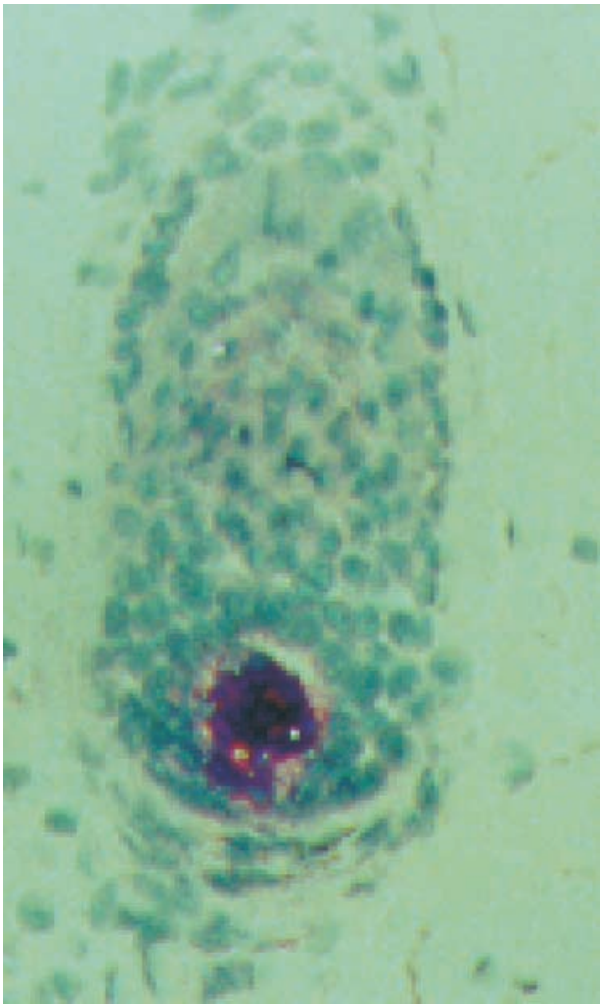

Figure 2 Steroid sulphatase immunoreactivity in human hair follicles: Immunohistochemical analysis using specific anti-steroid sulphatase antibody has been performed on sections of normal human skin. The steroid sulphatase immunoreactivity appears as a red stain. All sections were counterstained with haematoxylin. In this example a strong immunoreactivity in the dermal papilla can be seen in a human vellus hair (× 430).

other vertebrate species: human types I and II (Table 2); macaque; bovine; rat types I, II, III, and IV; mouse types I, II, III, IV, V and VI; hamster types I, II, and III.

Table 2 Characteristics of 3β-HSD isoenzymes.

Characteristics	Type 1 3β-HSD	Type 2 3β-HSD
Size (amino acids)	372	371
Chromosome localization	1p 13.1	1p 13.1
Gene (exons)	4	4

The importance of the 3β-HSD in male steroid hormone physiology is underscored by a genetically determined deficiency that is transmitted as an autosomal recessive trait and is characterized by varying degrees of salt wasting. Foetal testicular 3β-HSD deficiency causes undervirilized male genitalia (pseudohermaphroditism); women exhibit either normal sexual differentiation or mild virilization. At least 24 mutations have been identified in 25 distinct families with 3β-HSD deficiencies, leading to slightly different clinical phenotypes. All mutations were detected in the type II 3β-HSD gene. No mutation was detected in the type I 3β-HSD gene, which is expressed in peripheral tissues. Whether hair growth is affected in these individuals has so far not been investigated, but because of the importance of 3β-HSD in AM and increased activity in AGA this question warrants further investigations. Plucked hair follicles (without sebaceous gland) *ex vivo* also exhibit marked 3β-HSD activity and we were able to detect this enzyme mainly within the dermal papilla of anagen hair follicles.[26]

17β-hydroxysteroid dehydrogenases

Isoenzymes of 17β-HSD regulate levels of bioactive androgens and oestrogens in a variety of tissues. At present five isoenzymes of 17β-HSD that differ in tissue expression and requirements for cofactors such as NADPH for type III 17β-HSD, and NAD(+) for type 2 17β-HSD are known (Table 3). The importance of the type 3 enzyme in male steroid hormone physiology is underscored by the genetic disease 17β-HSD deficiency. Mutations in the type 3 17β-HSD gene impair the formation of testosterone in the foetal testis and give rise to genetic males with normal male Wolffian duct structures but female external genitalia very similar to

Table 3 Characteristics of 17β-HSD.

Characteristics	Type 1 17β-HSD	Type 2 17β-HSD	Type 3 17β-HSD	Type 4 17β-HSD	Type 5 17β-HSD
Size (amino acids)	327	387	310	736	323
Gene (exons)	6	5	11	–	9
Chromosome	17q21	16q24	9q22	–	10p14,15
Cofactor preference	NADPH	NAD +	NADPH	NAD +	NADPH
Catalytic preference	Reduction	Oxidation	Reduction	Oxidation	Reduction

the abnormalities seen in 5α-reducatase deficiency. These individuals are usually reared as females, but at puberty there is a striking rise in testosterone and they change their social sex. To date, more than 18 recessive mutations have been identified, giving rise to different clinical phenotypes. To our knowledge the presence or absence of AGA has so far not been investigated. However, potential significance of 17β-HSD isoenzymes in AGA is underscored by observations of Hodgins *et al.*[27] who plucked hair follicles from young adults not yet expressing AGA, but with a strong family history of baldness, and found two populations, one with high 17β-HSD activity and one with low enzyme activity. Therefore, linkage of the genes encoding the 17β-HSD isoenzymes and AGA warrants further investigation. Very early it was shown that plucked human hair follicles or hair follicles from stump-tailed macaques express considerable 17β-HSD activity because the principle metabolite of testosterone is androstenedione (Fig. 1). The isoenzyme-specific expression pattern in different parts of the hair follicle has so far not been investigated in detail primarily because of technical problems. Only one study described type 1 and 2 17β-HSD in the epithelial parts of the hair follicle. The authors did not find mRNA for 17β-HSD in the dermal papilla. However, at the protein level, this enzyme is metabolically active within the dermal papilla of anagen hair follicles.[28]

5α-reductases

The microsomal enzyme steroid 5α-reductase is responsible for the conversion of testosterone into the more potent androgen DHT and the conversion of androstenedione to 5α-androstanedione (Fig. 1). 5α-reductase deficiency is a rare autosomal recessive trait that was first described by Nowakowski and Lenz[29] but without aetiological characterization which was not possible at that time. In 1974 it became clear that these individuals lack functional 5α-reductase and today we know that the type 2 5α-reductase is lacking.[30–32] Several mutations of the gene that encodes type 2 5α-reductase have been described, but not every mutation will result in complete deficiency of the enzyme. Therefore, the clinical presentation of patients with 5α-reductase deficiency varies considerably. In typical cases, a 46, XY male who has testes, normal plasma testosterone and low DHT levels are observed. At birth a male ejaculatory system that terminates in a blind-ending vagina can be recognized together with a microphallus and a nonfused scrotum and maldescended testes. Therefore, these individuals display a female phenotype and are usually raised as girls. However, many affected individuals who were raised as females undergo a dramatic change of social sex at the time of expected puberty. They will have spermiogenesis, ejaculations and male-type sex drive. Interestingly, no or minimal beard growth or AGA is seen in these men. These observations together with the finding that both humans and stump-tailed macaques have beard and frontal scalp hair follicles with higher 5α-reductase activity than hair follicles from the occiput[12,33] indicates that the type 2 5α-reductase is involved in the pathogenesis of androgen-dependent hair growth. The inhibition of this isoenzyme is therefore a rational approach for treatment.

Table 4 Characteristics of 5α-R isoenzymes.

Characteristics	Type 1 5α-reductase	Type 2 5α-reductase
Size (amino acids)	259	254
Molecular weight	29 kDa	28 kDa
pH-optima *in vitro*	6–9	5,5
Chromosome localization	5p15	2p23
Gene (exons)	5	5

Two distinct 5α-reductase isoforms have been cloned. Subsequently it has been shown that these isoenzymes have distinct molecular, biochemical and tissue expression characteristics (Table 4). In humans mutations in the gene encoding type 1 5α-reductase have not been reported. In mice, however, a mutation in this gene will cause early foetal death because of oestrogen excess *in utero*.

Special attention has been paid to the dermal papilla and several authors have tried to localize both isoenzymes within the dermal papilla. Some authors were unable to find considerable 5α-reductase activity in occipital scalp dermal papilla, whereas others found this enzyme in beard and occipital scalp dermal papilla.[34,35] Recently, we were able to show that the main metabolic activity of type 2 5α-reductase can be detected in intact occipital scalp and beard dermal papilla.[36] Provided the dermal papilla plays a crucial role during androgen-mediated processes on the hair follicle, our results suggest that the dermal papilla might amplify testosterone-driven responses in the human hair follicle via the action of type 2 5α-reductase.

Oxidative 3α-hydroxysteroid dehydrogenases

Once formed, DHT is further inactivated via 3α-HSDs to the weaker androgens androsterone and androstanediol.

In theory the back conversion of these weak steroids to DHT via oxidative 3α-HSD may promote DHT-dependent hair loss. Recently we were able to demonstrate that such metabolism is present in the dermal papilla of occipital and beard hair follicles and theoretically any drug that is able to block this process might be beneficial for AGA (unpublished data).

Aromatase

The cytochrome P450 aromatase (P450arom) enzyme is required for bioconversion of androgens to oestrogens. Only a single human gene encoding aromatase P450 (CYP19) has been isolated. Mutations in the CYP19 gene do rarely occur and result in aromatase deficiency. Girls show pseudohermaphrodism at birth which sometimes is corrected by surgical repair of the external genitalia, including a clitoridectomy. At puberty, they develop virilization, pubertal failure with no signs of oestrogen actions, hypergonadotropic hypogonadism, polycystic ovaries on pelvic sonography, and tall stature. Males are tall with eunuchoid skeletal proportions. Their bone age is retarded and osteopenia can be observed, indicating that oestrogens are important for bone development. At puberty affected females will develop hirsutism due to an androgen excess and in theory females and males might develop early onset AGA. However, this question has not been reported or investigated.

Women tend to develop AGA later in life and in a milder form than men. With the decline of serum oestrogens during menopause many women show an accelerated progression of AGA. Oestrogens may play a protective role against the development of AGA, because pregnant women with high levels of oestrogens show a prolonged anagen phase, but lose their hair again post-partum. Recently it has been shown that hair follicles from women with AGA express more aromatase activity as compared with male-derived hair follicles,[37] and interestingly those women taking aromatase inhibitors tend to develop AGA rather rapidly.[38] These circumstantial lines of evidence indicate a role of aromatase in the pathogenesis of AGA. In order to unravel the pathways of oestradiol-mediated effects on the hair follicles, we measured aromatase activity in isolated intact human occipital hair follicles by incubating hair follicles and found aromatase to be expressed mainly within the root sheaths of the hair follicle. However, some cells of the stalk region of the dermal papilla also stained for aromatase. We also noticed that, in comparison with controls oestradiol-incubated female hair follicles showed a concentration- and time-dependent increase of aromatase activity. We concluded that an increased conversion of testosterone to 17β-oestradiol, and andros- tendione to oestrone, takes place in hair follicles derived from the occiput under the influence of estradiol. In theory, this pathway may diminish the amount of intrafollicular testosterone available for conversion to DHT.[39]

Interaction of DHT with AR and ARE

DHT is a pivotal trigger of androgen-mediated effects on the hair follicle and the principal signal transduction cascade: DHT- DHT/androgen receptor -ARE is similar in all hair follicles. However, DHT makes some hair follicles grow whereas others will miniaturize. Something fundamentally different must be present in beard vs. frontal hair follicle target cells. At present this paradox is not understood but an accumulating body of evidence indicates that the androgen receptor or distinct ARE might be involved in this process.

Androgen receptor

Without functionally active androgen receptors a genetically male foetus will not undergo normal male development *in utero* and a phenotypically female child is born. This is demonstrated by the various forms of androgen insensitivity syndrome (AIS). Several mutations in the gene for the androgen receptor may lead to AIS, but not every mutation will result in complete absence of functional androgen receptors. Interestingly complete AIS (grade 8) is characterized by a female phenotype despite a male genotype and lack of pubic hair, whereas incomplete AIS (grade 7) pubic hair is present. To our knowledge defined mutations of the androgen receptor and their effect on AGA have not been systematically looked for, but it is conceivable that some mutations may prevent balding. The literature on the localization of androgen receptors within the hair follicles is controversial because different antibodies located the androgen receptors in different compartments of the hair follicles. One group did not find androgen receptors in the dermal papilla and the hair follicle epithelium, whereas other groups described an intense staining for androgen receptors in the sebaceous gland, the dermal sheath and the outer root sheath of the hair follicles, as well as the dermal papilla in hair follicle of stump-tailed macaques, which is in accordance with results obtained in humans.[40] The different results were explained by different antibodies and different fixation techniques. Attempts to show differ-

ences in the quantitative concentrations of androgen receptors in bald vs. hairy scalp have yielded conflicting results. *In vitro* it has been shown that dermal papilla cells from an androgen sensitive body site contain more androgen receptors than dermal papilla cells from androgen-insensitive hair follicles.[40]

Androgen-responsive genes

After forming the DHT/androgen receptor complex and transport into the nucleus, this complex will bind to distinct DNA binding sites of androgen-susceptible genes. In the prostate DHT affects genes such as the prostate steroid-binding protein or testosterone-repressed prostate message (TRPM). By means of differential RT–PCR, androgen-responsive genes have been found in human foreskin fibroblasts and prostate smooth muscle cells. For the hair follicle, however, such mechanisms are almost unknown. This is mainly due to technical problems, because of the small size of single hair follicles and their intrafollicular compartments. In the prostate DHT induces 5α-reductase activity in an autocrine manner. Transforming growth factor-β1 has been shown to inhibit 5α-reductase in genital skin fibroblasts.[41] Conflicting results exist for insulin-like growth factor (IGF-1). This protein has been shown to induce 5α-reductase activity,[42] but other groups were unable to confirm these data.[43] *In vitro*, dermal papilla cells respond differently to exogenous testosterone, DHT, or estradiol.[44] Proliferation is inhibited by testosterone and DHT but not by estradiol. The physiologic significance of these data is difficult to interpret because *in vivo* dermal papilla cells do not proliferate. However, dermal papilla cells *in vitro* retain some of their *in vivo* parameters, and it has been shown that nexin-1 is not only present in the anagen hair bulb,[45] but also that this gene is regulated by androgens[46] which might indicate a role during the pathogenesis of AGA. Androgen-dependent hair follicles secrete soluble factors in response to testosterone such as IGF-1 that stimulate the growth of follicular epithelial cells[47] or inhibit the growth of complete hair follicles.[48] Other groups have reported on the secretion of stem cell factor[49,50] upon stimulation with testosterone. Whether this is of pathophysiological importance in AGA is not yet known. Recently the role of caspases have been stressed during the process of hair follicle miniaturization.[51]

Conclusions and future perspectives

AGA can be defined as a DHT-dependent process with continuous miniaturization of sensitive hair follicles. The type 2 5α-reducatase plays a central role through the intrafollicular conversion of testosterone to DHT. So far the predisposing genes for AGA are unknown and we do not understand the molecular steps involved in androgen-dependent beard growth vs. androgen-dependent hair loss. However, with the cloning of the entire human genome, we may have new resources to explore the etiopathogenesis of AGA in more detail. With increasing knowledge of the follicular repertoire of isoenzymes involved in androgen metabolism, new nontoxic and selective inhibitors may turn out to be fruitful therapeutic modalities. The same is true for selective androgen receptor blockers such as RU 58841,[48] or those drugs interfering with the DHT-dependent signal transduction cascade in hair follicles. We may also remember a statement by Van Scott and Ekel that was made more than 40 years ago: 'If the assumption is made that the size of a hair depends on the size of its papilla, a search for factors controlling the size of the papilla would seem to be appropriate in further investigations of male type baldness'.[20] It will be fascinating to see what will be launched for the treatment of AGA in the next few years. We will soon know the underlying genes, and this may give us the opportunity of a gene therapy targeting the hair follicle.

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