Male pattern hair loss: current understanding

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Introduction

The most common form of human hair loss is androgenic alopecia (AGA). It affects at least 50% of men by the age of 50 years and 50% of women by the age of 6o years. It is more obvious in men, and often manifests itself a decade earlier in men than in women.

Various historic observations have suggested that AGA in men, commonly referred to as male pattern hair loss, results from a combination of heredity and hormones. In 400 BCE, Hippocrates noted that neither eunuchs nor children became bald. Fifty years ago, Hamilton described the interdependence of androgens, genetic factors, and age which influence scalp hair growth. Until relatively recently, scientific observations have been obscured by anecdote and speculation, and not all medical and dermatologic textbooks have given hair loss serious consideration.

A better understanding of the molecular biology of hair growth in male pattern hair loss has indicated a new approach to treatment. This involves the inhibition of 5a-reductase, the enzyme which reduces testosterone to its more active form, dihydrotestosterone. Dihydrotestosterone is currently thought to be the most potent androgen affecting the human hair growth cycle, with adverse effects in male pattern hair loss. The current knowledge of normal scalp hair growth, hormonal and enzyme mediators, and the changes which occur in AGA, and which may be modulated by 5a-reductase inhibition, is summarized here.

Normal scalp hair

Anatomy in relation to growth

Normal anatomy
Hairs grow from follicles, which are invaginations of the superficial epithelium in the skin. On average, an adult scalp contains 100,000 follicles. The maximum number of hair follicles is present at birth. Thus the concentration of scalp hair follicles decreases as the head enlarges. Current biopsy data suggest that the estimated 700-750 follicles per cm- at birth decreases to approximately 318 per cm' in adult life.

Each hair is composed of the cortex, containing elongated, keratinized cells, surrounded by a cuticle of overlapping flattened cells with their free margins pointing upwards to the hair tip. Thick hairs may have a central medulla. Hair cells are produced from a matrix of specialized epidermal cells which surround a small invagination of dermis at the base of the follicle, known as the dermal papilla. Melanocytes in the bulb hair add pigment to newly formed cells.

The bulb also produces the inner root sheath, whose innermost cuticular layer, pointing downwards, interlocks with the cuticle of the anagen hair to anchor it in place. The outer root sheath is continuous with the surface epidermis, and enclosed by the glassy membrane. The entire follicle is surrounded by connective tissue, composed of fibroblasts and collagen and elastic fibers.

There are two basic types of human hair: vellus and terminal. Vellus hairs never contain a medulla, are fine and hypopigmented, have no obvious arrector pili muscle, and are scarcely visible, while terminal hairs are pigmented and relatively coarse. The diameter of a vellus hair does not exceed either 0.03 mm or the thickness of its inner root sheath.

Control of normal hair cycles

Normal hair cycle
Hair follicles show intermittent activity, with human hair growth occurring in cycles of three phases. The growth or anagen phase of human scalp hair lasts 2-7 years. During the anagen phase, the epidermal cells divide and grow, with a high metabolic activity rate, second only to that of hemopoietic tissue. Keratinized hair is continuously produced. Hair length depends partly on the growth rate, but mainly on the duration of the anagen phase, which varies with age and hair type. Vellus activity is shorter,

with an anagen duration of 6-12 weeks. On average, some 9o% or more of scalp hairs are in the anagen phase at any one time.

At the end of the anagen phase, hair growth ceases, and the catagen phase begins. On average, 1% of scalp hairs will be in this phase, which lasts several weeks. During catagen, the hair follicle becomes thinner, due to a volumetric reduction of the external root sheath by apoptotic cell death. The melanocytes in the bulb stop producing melanin, becoming histologically indistinguishable from other cells in the matrix. The ascending hair bulb gradually loses its internal and external root sheaths, and acquires a club-shaped end, with underlying trichilemmal keratin. The dermal papilla separates from the epidermal cells and the connective tissue sheath. Thickening of the glassy membrane occurs, and the epidermal column lengthens, following the club hair towards the surface of the skin.

Terminal scalp hair then enters the resting or telogen phase for an average of 3 months. The epidermal column shortens until it forms a small protuberance called the secondary germ. After recommencement of the anagen phase, the secondary germ grows downwards and invaginates the dermal papilla, forming a new hair bulb. A new hair emerges by the side of the old club, which then falls out.

The signals for change from one phase to the next remain poorly understood, although it has been suggested that perhaps a mitotic inhibitor accumulates during the anagen phase, and is dispersed during the telogen phase. A hair growth inhibitor has been described in telogen in mice. Hair growth shows seasonal and environmental fluctuations. Scalp growth has been shown to peak in spring and reach a nadir in autumn; other body hair shows different seasonal variation. This may be influenced via the hypothalamus, responding to changes in sun exposure and ambient temperature.

Hormones as modulators of normal hair growth
The distribution of hair, as well as its type, growth rate, and follicular cycle, is mediated, at least in part, by complex hormonal regulatory mechanisms, which are only partly understood. It is known that the hypothalamus, pituitary hypophysis, adrenal cortex, thyroid, and gonads are all involved. Androgens are the major determinants of hair distribution in both sexes. Axillary and lower pubic hair is dependent upon adrenal androgen, while testicular androgen is required for upper pubic, ear, facial, and truncal hair. Androgens also influence the type of hair produced. For example, after puberty, some axillary and pubic vellus hairs become terminal hairs in response to androgens.

The metabolism of testosterone to dihydrotestosterone by 5a-reductase is clearly important in the regulation of

hair growth, as deficiencies of facial and body hair and persistence of scalp hair occur at low levels of 5a-reductase. Dihydrotestosterone appears to be necessary for androgen-mediated action on the hair follicle, as testosterone itself binds to the androgen receptor with a lower affinity. Thus, testosterone acts as a pre-hormone in specific androgen-dependent target areas. Dihydrotestosterone, once formed, has a differential effect on hair growth at different sites. The importance of the conversion of testosterone to dihydrotestosterone for hair growth is supported by the observation that, in patients with celiac disease, the rate of beard growth correlates with the plasma levels of dihydrotestosterone, but not testosterone.

It is now known that two separate isoenzymes Of 5a-reductase exist. Type 1 is found predominantly in scalp skin, sebaceous glands, chest/back skin, liver, adrenal gland, and kidney, whereas Type 2 has been specifically localized within the hair follicle itself, in the innermost layer of the outer root sheath. It is also the predominant form in the prostate and beard. All hair follicles show some 5a-reductase activity, although this is 3-8 times greater during the anagen phase than in resting follicles.

Testosterone and dihydrotestosterone can circulate systemically to follicles, or be manufactured locally in the follicle from circulating weak androgens (dehydroepiandro-sterone and androstenediol) via complex enzyme-mediated processes involving specific dehydrogenase and reductase enzyme pathways.

In the scalp, the principal metabolite from testosterone is dihydrotestosterone, although some testosterone may also be oxidized to androstenedione. 3a-Hydroxysteroid dehydrogenase converts dihydrotestosterone to the less potent androstenediol. All of these enzyme reactions are dependent upon specific pyridine cofactors. It is clear that reductase, dehydrogenase, and probably aromatase enzymes are of major importance in hair growth as they mediate the complex interchange of sex hormones implicated in anagen activity.

There is direct evidence for the role of testicular androgen in the regulation of hair growth. In humans, all hair growth requires androgenic stimuli, except that on the scalp (even though all scalp hair follicles have androgen receptors). In genetically susceptible subjects, some hair follicles in the frontal and vertex regions of the scalp respond to androgens by a reduced length of the anagen phase, and regression of the follicles to produce finer, thinner hairs.

Exactly how androgens modulate normal hair growth is not fully understood, although it is clear from the physiology and biochemistry that they play a central role. Androgens stimulate the production of growth factors and proteases, affect angiogenesis, basement membrane proteins and cell metabolism, and appear to shorten the

the anagen phase of growth. Each hair follicle, regionally as well as locally, appears to be independently genetically regulated to respond to androgens. This may be achieved either by variations in androgen metabolism at different sites, or by variations in androgen receptor density or sensitivity. It has now been shown that the androgen receptor density in men and women with AGA is greater in the frontal than in the occipital area.

Other modulators of normal hair growth
An active group of stem cells has been found high in the bulge area of mouse hair follicles. It has been suggested that such cells may be involved in triggering the progression through the hair growth phases.

On a cellular level, interleukin-i (IL-i) has been shown to be a potent inhibitor of human hair growth in vitro, and the aberrant expression of IL-iB has been found in alopecia areata. It has been suggested that the histologic changes seen in male pattern hair loss are suggestive of inflammation.

Male pattern hair loss

Pathophysiology
Male pattern hair loss occurs in a characteristic pattern affecting the front-vertical scalp, which has been described elsewhere. Hairs in the affected area become progressively finer and less pigmented until they appear like vellus hairs; however, they may be distinguished from true vellus hairs by the presence of remnants of the arrector pili muscle and long follicular streamers.

The anatomy of bald or balding scalp shows various changes which have been well documented. Regardless of age, balding scalps have a reduced density of terminal hair follicles when compared with non-bald people of the same age. Those aged *30-90* years with normal hair have been reported to have *459* follicles per cm', compared with *3o6* in male pattern hair loss. Recent data suggest that follicular counts in normal adults average *326* per crn2 and, in those with AGA, 278 per cm2. Total scalp thickness is reduced, due to substantial thinning of the subcutaneous adipose layer.

The progressive miniaturization of hair follicles in AGA is reflected in the histopathologicchanges, which are similar in men and women. Terminal hairs become vellus-like, and hair roots retreat upwards so that many miniaturized hair bulbs are found in the mid or papillary dermis. The Position of the original terminal follicle is indicated by a follicular streamer (stelae or fibrous tracts) extending from the subcutaneous tissue up the course of the follicle to the miniaturized hair. AGA is therefore characterized by decreased terminal hairs and increased follicular streamers and vellus-like hairs.

Table 1 Characteristics of hairs in AGA and controls

	AGA	Controls
No. terminal hairs	23	35
No. vellus-like hairs	12	5
Ratio terminal : vellus like	2 : 1	7 : 1
Anagen : telogen (%)	83 : 17	93.5 : 6.5

Horizontal sections of 4mm punch biopsy from alopecic and normal scalp.

The progressive reduction in the duration of anagen but not telogen causes a relative increase in telogen hairs (see Table 1). In a 4-mm punch biopsy of AGA, the average follicular count in a horizontal section gave a terminal hair to vellus-like hair ratio of 2 : 1, while normal controls have a terminal to vellus-like ratio of 7 : 1. A terminal to vellus-like ratio of less than 4 : 1 is likely to indicate increased follicular miniaturization. The significant reduction in total follicular counts seen in 10% of cases of AGA indicates that only a minority of patients have a decreased capacity for possible future regrowth.

One study has indicated that areas of the scalp that lose hair in men may have a microvascular insufficiency, leading to local tissue hypoxia, compared with hair-bearing scalp. A mild perifollicular lymphohistiocytic infiltrate, mainly around the upper follicle, but sometimes involving the lower follicle, is also seen in both one-third of cases of AGA and in normal controls. A moderate or dense lymphohistiocytic infiltrate, often with concentric layers of collagen, is seen in *40%* of cases of AGA, but only in 10% of normal controls, and may lessen the response to topical minoxidil 2%. Occasional mast cells, eosinophils, and even foreign body giant cells may be seen. Sebaccous glands remain intact.

Etiology
Genetics
The genetic predisposition to male pattern hair loss is still poorly understood. Although there is agreement that it is an inherited condition, it may not be genetically homogeneous. Current standard textbooks contain authoritative but conflicting statements. Any genetic hypothesis for male pattern hair loss must account for the strong autosomal inheritance; this has been suggested to be due to a single, autosomal dominant gene, or to a single pair of sex-linked factors. The latter theory was supported by studies of family history and gene frequency. Later, it was suggested to be due to a dominant gene with increased penetrance in men, or variable penetrance. Others believe it to be multifactorial.

Observations have pointed to specific genetic abnormalities associated with the presence or absence of male pattern

hair loss, but causal relationships are not clear. A large family with a strong history of male pattern hair loss contained two subpopulations distinguishable on the basis of i7B-hydroxysteroid activity: those with low levels retained their hair. In a number of genetic diseases, there is an absence of male pattern hair loss, In testicular feminization syndrome, for example, the specific defect is end-organ insensitivity to androgens due to the absence of androgen-binding mechanisms (androgen receptors). Male pattern hair loss does not occur in such people.

Attempts to associate male pattern hair loss with increased or decreased susceptibility to other diseases have not been conclusive. Male pattern hair loss has been reported to be associated with higher serum cholesterol and blood pressure, although the association with cholesterol, but not with blood pressure, becomes weaker with increasing age. A link with increased coronary heart disease risk is stronger for younger men: in a study of men aged less than 55 years, severe hair loss was associated with death from ischemic heart disease, although there was also a weaker association with the overall incidence of ischernic heart disease. Rapid hair loss in men has also been suggested to be a marker for coronary disease.

Aging

It is important to distinguish hair changes which occur with normal aging, known as senescent baldness, from male pattern hair loss. Male pattern hair loss has been described as a genetically determined disorder of unknown etiology which is distinct from the hair thinning normally associated with aging; however, the clinical and histologic evidence for senescent alopecia is not clear cut and is still disputed.

Role of Androgens

General. Although it has been known for over 2ooo years that eunuchs do not suffer from male pattern hair loss, there is now direct evidence for androgen involvement. Men who have undergone prepubertal castration do not develop male pattern hair loss, but it can be induced by testosterone in those individuals who are genetically susceptible. This has been shown in an identical twin study, where one twin was castrated prepubertally, and retained his hair, while the other twin showed male pattern hair loss. When the castrated twin was given testosterone, male pattern hair loss rapidly ensued. Postpubertal castration does not prevent the development of male pattern hair loss, and it is thought that the magnitude of the response to androgens may be determined by a genetic "switch" triggered at puberty.

Until recently, it was not known whether male pattern hair loss was due to excess androgen or an enhanced peripheral response. Some men with male pattern hair loss

have normal plasma testosterone, but lower levels of sex hormone-binding globulin, and higher salivary testosterone, suggesting that they may have more available free testosterone.

Type 2 5a-reductase activity. There is now evidence that dihydrotestosterone is the active androgen in male pattern hair loss. It has been shown that men with male pattern hair loss have increased 5a-reductase activity in their hair follicles, and that male bald scalp has an increased capacity to convert testosterone to dihydrotestosterone.

Deficiency of 5a-reductase occurs in male pseudohermaphroditism. Here, testosterone secretion is normal, but dihydrotestosterone levels are decreased. As the androgen receptors function normally in this condition, testosterone is able to bind to them and provide normal sexual function with adequate libido, erectile function, and semen production, but dihydrotestosterone production is severely limited in prostate and scalp, with low circulating levels. The affected individuals have no facial or body hair, do not show temporal hairline recession or vertex balding, have normal scalp hair, and their prostate glands remain small. These individuals are deficient in Type 2 5a-reductase, a finding that has led to the suggestion that this isoenzyme is probably involved in male pattern hair loss. This hypothesis is not entirely consistent with the observation that the Type i isoenzyme (which is unaffected in male pseudohermaphrodites) is the predominant 5a-reductase in the scalp of normal postpubertal males. Several recent studies, however, have confirmed that Type 2 5a-reductase is present in and around normal scalp hair follicles. The predominance of Type 1 5a-reductase on volumetric analysis of scalp skin is probably due to its presence in sebaceous glands.

Androgen conjugation. Not only is there enhanced 5a-reductase activity in male pattern hair loss, but there may also be a disorder of androgen conjugation, favoring sulfurylation over glucuronidation. In one study, serum hormone conjugate levels were measured in prematurely balding men and normal male controls. Those with androgenic hair loss had lower levels of 3a-androstenediol glucuronide than controls; the ratio of 3a-androstenediol glucuronide to 3a-androstenediol was significantly reduced and the ratio Of 3a-androstenediol sulfate to 3a-androstenediol glucuronide was raised in comparison with controls.

Androgen receptors. In men with male pattern hair loss, testosterone and dihydrotestosterone both bind to the androgen receptor in the hair follicle, although dihydrotestosterone binds more avidly. The resulting complex migrates to the cell nucleus and binds to chromatin acceptor sites, affecting the action of ribonucleic acid (RNA) polymerase and subsequent protein synthesis. Differences in the number, type, and affinity of androgen receptors found

in different hair follicles may be due to endogenous regional proteins found in hair follicle cells. A peptide inhibitor protein is found in anagen hair follicle cells, and regulates binding to the androgen receptor in a noncompetitive way. A converting factor is also found in the anagen follicle cells. It has sulfhydryl oxidative-reductive capacity, and influences binding on the receptor to produce a less active complex.

Once in the nucleus, the hormone-receptor complex binds to specific deoxyribonucleic acid (DNA) sites adjacent to genes affecting hair growth. Age-related proteins, androgens, and other compounds can occlude certain gene sites, and so may affect cell growth as aging occurs.

Other mechanisms. Other important hormonal mechanisms which operate in male pattern hair loss are less well understood. The hormone levels of men with male pattern hair loss are within the normal range, although increases in serum cortisol levels can occur. Some believe that androgenic hair loss is exacerbated by stress, which also causes increases in cortisol

Some men with male pattern hair loss have also been reported to differ from age-matched controls in serum levels of androstenedione, 17B-estradiol, and luteinizing hormone. Suprarenal stimulation, as well as hypophyseal feedback mechanisms, may be involved here.

Conclusions

Hair growth is under complex genetic and hormonal control, regulated predominantly by androgens. Androgenic control of hair growth, and of male pattern hair loss, is mediated through a final common pathway involving the enzyme 5a-reductase.

Men with male pattern hair loss have increased 5a-reductase activity in their hair follicles, and the male bald scalp has an increased capacity to convert testosterone to the more potent dihydrotestosterone. There is increasing evidence that Type 2 5a-reductase activity plays an important role in this condition.

The current range of antiandrogens, such as cyproterone, spironolactone and flutamide, cannot be given systemically to men as they block androgen receptors and prevent the action of both testosterone and clihydrotestosterone, resulting in castrate effects with loss of sexual function. The inhibition of 5a-reductase, however, prevents the formation of dihydrotestosterone without significantly affecting testosterone, so that sexual activity is unaffected. It is therefore possible to give a man a suitable 5a-reductase inhibitor orally without interfering with his sexual potency. Various drugs have been and are being developed to inhibit both Type 1 and 2 5a-reductase. Judging from male Pseudohertnaphrodites, who have an absence of Type 2 5a-reductase and never lose their hair, it is logical to treat

and prevent male pattern AGA with a drug which is a selective inhibitor of Type 1 5a-reductase. Finasteride is such a drug, and is now known to be safe and effective for male pattern hair loss. Other inhibitors of both Type 1 and 2 5a-reductase are under development. These drugs are the result of genetic engineering being used to overcome molecular defects.

Advances in our understanding of the complicated mechanisms involved in the control of hair growth, and in receptor pharmacology as applied to the hair follicle, are opening up interesting new possibilities for therapeutic intervention in male pattern hair loss. Future research should explore these to determine whether there is, at last, a real possibility to influence this potentially disturbing disorder.