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Androgens and alopecia

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Abstract

Androgens have profound effects on scalp and body hair in humans. Scalp hair grows constitutively in the absence of androgens, while body hair growth is dependent on the action of androgens. Androgenetic alopecia, referred to as male pattern hair loss (MPHL) in men and female pattern hair loss (FPHL) in women, is due to the progressive miniaturization of scalp hair. Observations in both eunuchs, who have low levels of testicular androgens, and males with genetic 5α-reductase (5αR) deficiency, who have low levels of dihydrotestosterone (DHT), implicate DHT as a key androgen in the pathogenesis of MPHL in men. The development of finasteride, a type 2-selective 5αR inhibitor, further advanced our understanding of the role of DHT in the pathophysiology of scalp alopecia. Controlled clinical trials with finasteride demonstrated improvements in scalp hair growth in treated men associated with reductions in scalp DHT content, and a trend towards reversal of scalp hair miniaturization was evident by histopathologic evaluation of scalp biopsies. In contrast to its beneficial effects in men, finasteride did not improve hair growth in postmenopausal women with FPHL. Histopathological evaluation of scalp biopsies confirmed that finasteride treatment produced no benefit on scalp hair in these women. These findings suggest that MPHL and FPHL are distinct clinical entities, with disparate pathophysiologies. Studies that elucidate the molecular mechanisms by which androgens regulate hair growth would provide greater understanding of these differences.

Keywords: Androgenetic alopecia; Dihydrotestosterone; Male pattern hair loss; Female pattern hair loss; Finasteride

1. Introduction

The term *androgenetic alopecia* (AGA) is often used to describe the patterned loss of scalp hair in genetically susceptible men and women. This condition is also known as male pattern hair loss (MPHL), or common baldness, in men and as female pattern hair loss (FPHL) in women. Alopecia in these cases is characterized by thinning of hair as opposed to follicular loss, at least in early stages (Price, 1975; Whiting, 1993). In men, MPHL does not present until after puberty, usually becoming manifest in the third decade and in almost all cases by the fourth decade of life (Hamilton, 1942, 1951). MPHL typically begins with bitemporal recession, followed by progressive thinning in the frontal and vertex areas of the scalp; recession of the frontal hairline is common. Over time, the frontal and vertex thinning areas may merge, resulting in near complete visible hair loss over the top of the scalp. In contrast, FPHL may present as late as the sixth decade of life (Olsen, 2001) and is characterized by diffuse thinning in the frontal and parietal areas of the scalp; preservation of the frontal hairline is the norm. Hair over the occipital scalp is preserved in both sexes. Unlike MPHL in men, complete baldness in affected regions of the scalp is rarely observed in premenopausal women with FPHL. Postmenopausal women, however, may develop, or progress to, a pattern of hair loss more characteristic of men with MPHL (Venning and Dawber, 1998).

Until recently, it has generally been assumed that both MPHL and FPHL result from an abnormal sensitivity of scalp hair follicles to circulating androgens. Hair loss in either sex is characterized by the progressive transformation of thick, pigmented terminal hairs into short, fine, hypopigmented vellus-like hairs. However, clinical trials with finasteride, a type 2 5α-reductase (5αR) inhibitor, suggest that the pathophysiology of patterned scalp hair loss in women differs from that in men. The purpose of this paper is to review recent advances in our understanding of the role of androgens

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in the pathophysiology of common scalp hair loss in men and women.

2. Androgens and hair growth

Androgens are mediators of terminal hair growth throughout the body (Fig. 1). Without androgens or their activity, scalp hair grows constitutively while body hair growth is inhibited, as demonstrated by males with androgen insensitivity (testicular feminization) (Griffin and Wilson, 1989). With androgen activity, those genetically predisposed develop scalp alopecia, manifested as miniaturization of scalp hair follicles in a defined pattern. In contrast, with sexual maturity androgens cause enlargement of vellus hairs to form terminal follicles in the axilla and pubis in both sexes, and on the face, chest and extremities in men. Excess androgen action can cause unwanted hair growth (hirsutism) in women. The seemingly paradoxical effects of androgens on scalp and body hair are not well understood. However, androgen effects on hair growth at particular body areas are believed to be due, at least in part, to factors such as increased number of androgen receptors, increased local production of high-potency androgens, and/or reduced degradation of androgens.

The pathway of steroid hormone metabolism studied most thoroughly in relation to hair growth is the peripheral conversion of testosterone to dihydrotestosterone (DHT), a reaction catalyzed by the enzyme 5αR (Wilson and Gloyna, 1970; Kaufman, 1996). Compared to testosterone, DHT has approximately fivefold greater affinity for the androgen receptor. In some androgen-sensitive target tissues (e.g. prostate), DHT rather than testosterone appears to mediate aspects of androgen action, consistent with high tissue concentrations of the metabolite. There are two distinct forms of 5αR, referred to as types 1 and 2, which differ in their tissue distribution (Thigpen et al., 1993; Russell and Wilson, 1994; Ellsworth and Harris, 1995). Type 1 5αR is prominent in sebaceous glands, while type 2 5αR is prominent in the genitourinary tract and within hair follicles, in the outer root sheath and proximal part of the inner root sheath (Bayne et al., 1999). Other studies have suggested that type 2 5αR may also be the predominant form of this enzyme in dermal papillae (Eicheler et al., 1995; Hoffmann and Happle, 1999). Both 5αR isoenzymes are expressed in the liver, contributing to circulating levels of DHT.

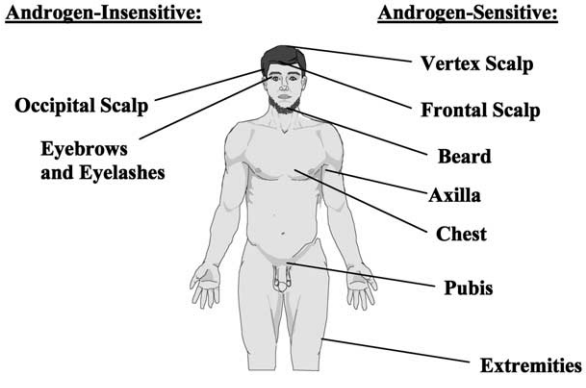

Fig. 1. Schematic showing the differential effects of androgens on hair growth. Androgens have diametrically-opposed effects on hair growth, depending on body location: on the beard, chest, pubic, axillae and extremities, hair follicles are stimulated to become terminal follicles, beginning at puberty; on the scalp, follicles are inhibited in a patterned distribution in men with a hereditary predisposition to baldness.

Definitive evidence of a role for 5αR in hair growth was provided by reports in 1974 describing subjects with genetic mutations affecting expression of the type 2 5αR enzyme. Patients with these mutations had marked reduction in DHT formation, with preservation of testosterone levels (Imperato-McGinley et al., 1974; Walsh et al., 1974). Males homozygous for this mutation were easily identifiable, as they were born with a specific phenotypic form of pseudohermaphroditism. However, the marked increases in circulating androgens that normally occur during puberty produced virilization and development of normal libido and male phenotype (muscle and skeletal mass) in these subjects. Of note, these men had sparse facial and body hair and appeared to be protected from developing prostate enlargement and patterned hair loss later in life (Imperato-McGinley et al., 1974; Kuttenn et al., 1979). These findings provided strong evidence that while type 2 5αR plays an essential role in normal male genital development in utero, in adulthood it appears to have no beneficial physiological role, but rather is implicated in the pathogenesis of a variety of androgen-dependent disorders in adult men. Female subjects with 5αR deficiency were phenotypically normal, but could be detected by biochemical assay (Imperato-McGinley et al., 1974; Katz et al., 1995).

At present, little is known about the role, if any, of type 1 5αR on hair growth. Unlike type 2 5αR, a human type 1 5αR genetic deficiency syndrome has not been identified, and the role of this isoenzyme in human physiology is unclear. The discovery of high levels of type 1 5αR activity in sebaceous glands, particularly in acne-prone regions of the face and chest, suggest that this enzyme may play an important role in the regulation of sebum secretion (Thiboutot et al., 1995). While males with androgen insensitivity syndrome have markedly reduced levels of sebum production, patients with type 2 5αR deficiency have normal sebum output, further supporting a role for the type 1 enzyme in sebum secretion (Imperato-McGinley et al., 1993).

3. Hair follicle cycling in alopecia

The hair follicle, an invagination of the skin with continuously proliferating specialized matrix cells at its base, is responsible for producing the keratin proteins that comprise a strand of hair. Pigmentation of the hair fiber depends on melanocytes, which are situated in the matrix area and deposit melanin into the growing hair shaft. The normal hair cycle consists of three distinct stages, termed the anagen growth phase, catagen involution phase, and telogen resting phase (Ebling, 1987; Stenn and Paus, 2001). The anagen period of active growth is followed by the short catagen transition phase, during which much of the hair follicle undergoes programmed cell death (Cotsarelis, 1997). This is followed by the telogen phase, in which there is regrowth of follicular germinal cells, until a new hair begins to form and the cycle repeats itself.

Typical patterned scalp hair loss in men and women is caused by aberrations in the growth cycle and subsequently in the morphology of scalp hair follicles. In a normal adult scalp, the anagen phase lasts from two to as long as 7 years. However, in men with MPHL, the duration of anagen decreases from several years to months or weeks, while the telogen phase remains the same or lengthens (Jackson, 2000). Because affected hairs cycle more quickly, due to the decreased duration of anagen, there is a corresponding increase in the number of telogen hairs. This leads to a marked reduction in the anagen-to-telogen ratio from a normal 6 to 8:1 ratio to an abnormal 0.1 to 3:1 ratio (Whiting, 1993). Telogen hairs are more easily plucked than anagen hairs, thus explaining the increased hair shedding commonly noticed by patients during brushing and shampooing. Moreover, the lag period between the telogen and anagen phase becomes progressively longer, leading to a reduction in the number of hairs present on the scalp at any one time (Courtois et al., 1994).

Concomitant with changes in the hair growth cycle, affected hairs undergo a process termed *follicular miniaturization*, in which large terminal hairs are transformed into thin, vellus-like hairs (Fig. 2). The transformed follicles produce finer hair fibers that lack pigmentation, with reduction in hair diameter from a minimum of 0.08 to <0.06 mm (Rushton et al., 1991). When a hair follicle miniaturizes, it ascends upward from the reticular dermis to the papillary dermis, and is followed by an associated angiofibrotic tract called a follicular streamer (Kligman, 1988). The transformed follicle cycles up and down through anagen and telogen in the papillary dermis as a small, cosmetically-insignificant vellus-like hair. An effective treatment for this type of hair loss should stimulate a miniaturized, vellus-like hair to transform back into a terminal one (Whiting et al., 1999). When this occurs, the miniaturized hair travels back down the streamer tract to the reticular dermis to resume its position and role as a terminal hair.

While follicular miniaturization is a pathognomonic feature of patterned hair loss in both sexes, there are differences in the degree and pattern of miniaturization over affected regions of the scalp. Whiting et al. (1999) examined serial punch biopsies taken from transitional areas of hair loss over the vertex balding area in men, and in the area of frontal/parietal thinning in women. The degree of miniaturization in postmenopausal women, as measured by the changes in anagen-to-telogen ratios, was not as extensive as that observed in men. Furthermore, women often present with a mosaic pattern of variable-diameter hairs in affected regions of the scalp (Maguire and Kligman, 1963; Olsen, 2001), whereas men typically demonstrate a more homogeneous pattern of miniaturization.

4. Evidence of a role for androgens in the pathophysiology of alopecia

Androgens are steroid hormones that bind to nuclear receptors to effect genetic transcriptional events. In men with MPHL, follicular miniaturization is caused by an inherited sensitivity of scalp hair follicles to normal levels of circulating androgens. The genetic and androgenic basis of the condition, as well as its typical patterned phenotype, were well-documented by Hamilton in a series of seminal articles (Hamilton, 1942, 1951). In these studies, prepubertal castration resulted in the retention of a juvenile hairline while postpubertal castration led to phenotypes more consistent with the general population, with typical MPHL in some patients. Regardless of the age of the patient at the time of castration or the degree of baldness at initial observation, none of the castrated patients demonstrated progressive hair loss over a year of observation. Administration of exogenous testosterone to these castrated men, even at sub-physiologic replacement doses, produced typical, progressive, patterned balding. Patients whose scalp hair was resistant to the effects of testosterone administration were found in families without a significant history of baldness, suggesting that a genetic predisposition was required for the development of androgen-induced scalp hair loss. Taken together, Hamilton's observations established that testosterone, or one of its metabolites, was involved in the development of MPHL and that a genetic component appeared necessary for its expression. Hamilton did report cases of women with scalp hair loss and virilization due to androgen-secreting tumors, but these observations did not provide evidence for a genetic and/or hormonal basis for common FPHL in which virilization is not commonly observed.

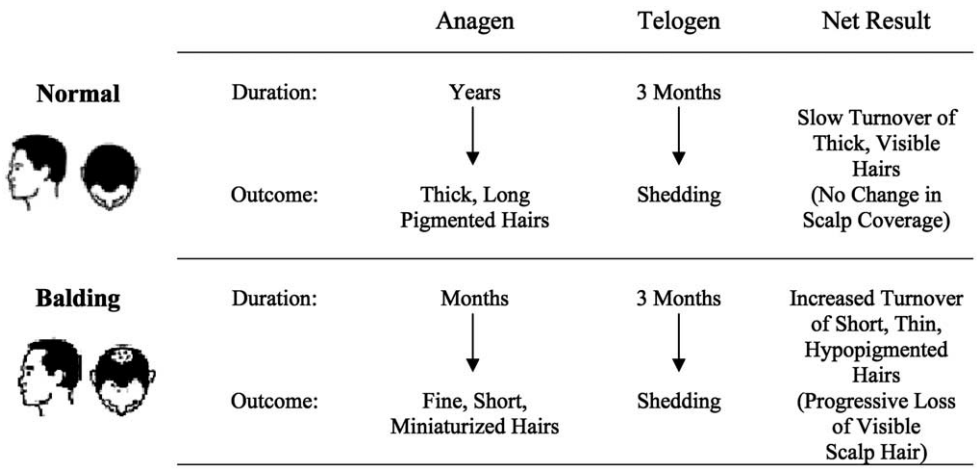

Fig. 2. The dynamics of hair follicle cycling in normal and balding scalp. In a normal scalp, the average duration of the anagen growth phase is several years and that of the telogen phase 3 months. In patients with MPHL, the hair growth cycle is altered, producing a progressive reduction in the duration of the anagen phase. This results in the production of short, thin, hypopigmented, cosmetically-insignificant hairs that are perceived as loss of hair.

5. What are the specific androgens involved in alopecia?

Since Hamilton's work, the key observation implicating a specific androgen in the pathophysiology of MPHL in men is based on the observation that male subjects with genetic deficiency of type 2 5αR do not develop scalp hair loss (Imperato-McGinley et al., 1974; Kuttenn et al., 1979). This protective phenomenon occurs despite the subjects' having normal or even slightly elevated levels of circulating testosterone. Thus, it appears that in balding men DHT binds to androgen receptors in susceptible hair follicles and, by an unknown mechanism, activates genes responsible for follicular miniaturization. In agreement with this hypothesis, both plucked follicles and skin from balding scalp have been shown to contain increased levels of DHT compared to follicles and skin from non-balding scalp (Schweikert and Wilson, 1974; Dallob et al., 1994).

6. Studies of finasteride in the treatment of male pattern hair loss

Further evidence in support of the DHT-dependence of MPHL comes from clinical trials with finasteride, a type 2-selective inhibitor of 5αR, in men with MPHL. In initial clinical studies, finasteride treatment reduced scalp DHT in balding patients in a dose-dependent manner (Drake et al., 1999). The efficacy and safety of finasteride treatment in men with MPHL was subsequently established in three large, Phase III, multicenter trials. Two of these studies enrolled men with predominantly vertex hair loss (Kaufman et al., 1998; Finasteride Male Pattern Hair Loss Study Group, 2002), while the third study enrolled men with predominantly frontal (anterior-mid scalp) hair loss (Leyden et al., 1999).

6.1. Phase III vertex studies

The safety and efficacy of finasteride in men with vertex scalp hair loss was established in two, 1-year, placebo-controlled studies which continued as four consecutive, 1-year, placebo-controlled extension studies (Kaufman et al., 1998; Finasteride Male Pattern Hair Loss Study Group, 2002). The studies enrolled 1553 men, aged 18–41 years, with mild to moderate hair loss in the vertex scalp who were randomized to treatment with finasteride 1 mg/day or placebo. The analysis of data of the 5-year study period demonstrated that long-term treatment with finasteride led to significant and durable improvements in scalp hair growth in men with MPHL compared to treatment with placebo. Efficacy was established through a comprehensive set of predefined endpoints: hair counts, obtained in a defined, representative 1-inch diameter circular area of scalp hair loss at the anterior leading edge of the vertex bald spot; patient self-assessment of scalp hair growth, based on a validated questionnaire; investigator clinical assessment of scalp hair growth; and assessment of standardized clinical photographs of the head by an expert panel.

Based on the assessment of standardized clinical photographs by the expert panel, 48% of men treated with finasteride demonstrated improvement in hair growth at 1 year, compared with 7% of men receiving placebo. This clinical benefit of finasteride was sustained over the study period, such that 48% of men on finasteride and 6% of men on placebo were rated as improved at 5 years by the expert panel. Equally significant, 75% of patients treated with placebo had visible worsening in scalp hair coverage at 5 years, compared with 10% of those treated with finasteride.

The improvements observed from analysis of clinical photographs in patients receiving finasteride were asso-

ciated with improvements in hair count (mean baseline hair count ± SE = 876 ± 11 hairs). For patients receiving finasteride, there was an 11% mean increase from baseline hair count at 1 year, with significant improvement above baseline maintained over 5 years. In contrast, the placebo group progressively lost hair, confirming the progression of hair loss due to continued miniaturization of scalp hair. The net treatment effect of finasteride relative to placebo increased progressively over time, leading to a net improvement of 277 hairs in the target area compared to placebo at 5 years. Moreover, most (65%) finasteride-treated men had increases in hair count relative to baseline at 5 years compared to none of the placebo-treated men. These data support the conclusion that the progression of hair loss observed in placebo-treated men was significantly reduced by finasteride.

The clinical relevance of the improvements observed by both clinical photography and hair count was further supported by the patient self-administered hair growth questionnaire. Men treated with finasteride had a more positive assessment of their hair growth and satisfaction with their appearance than men treated with placebo, with the majority of finasteride-treated men reporting satisfaction with the overall appearance of their scalp hair at 5 years. Lastly, the investigators' clinical assessment demonstrated a sustained benefit of finasteride treatment over time, with 77% of drug-treated patients rated as improved at 5 years compared to 15% of those on placebo.

The data from these studies represent the longest reported controlled observations in men with MPHL. The results of these studies demonstrate that long-term treatment with finasteride leads to significant and durable improvements in scalp hair in men with MPHL. In contrast, data from the placebo group confirmed that, without treatment, progressive reductions in scalp hair count and continued loss of visible hair occur. Side effects of finasteride treatment were limited to transient sexual dysfunction in a small number of men, each occurring in $<2\%$ of treated subjects.

6.2. Phase III frontal hair loss study

The frontal hair loss study was conducted in parallel with the studies in men with predominantly vertex hair loss in order to evaluate the efficacy of finasteride 1 mg primarily in the anterior-mid scalp area after 1-year of treatment (Leyden et al., 1999). This study used similar endpoints to those used in the vertex studies and demonstrated significant improvements in all efficacy measures with finasteride compared with placebo. During the first year, 70% of finasteride-treated patients demonstrated no further frontal hair loss relative to baseline, while 56% of patients on placebo lost hair by hair count. Finasteride treatment also led to significant clinical improvement, as assessed by patients, investigators, and the expert panel assessing standardized clinical photographs. The results of this study demonstrate that treatment with finasteride produces significant improvements in hair growth in the anterior-mid scalp area in men with predominantly frontal hair loss.

6.3. Scalp biopsy study

A scalp biopsy study was conducted in a cohort of patients from one study center in the Phase III vertex studies to determine the effect of finasteride on hair growth as evaluated by histological analysis. This study was conducted in 26 men, age 18–41 years, with mild to moderate vertex hair loss (Whiting et al., 1999). Serial punch biopsies were taken from the transitional area of hair thinning in the vertex scalp at baseline and 1-year. In this small cohort study, finasteride treatment led to a trend towards improvement in the terminal-to-vellus ratio compared to no change in the placebo group, suggesting that finasteride treatment tended to reverse the process of follicular miniaturization in balding men.

6.4. Study in monozygotic male twins

Recently, a small ($n = 18$), 1-year, placebo-controlled trial of finasteride 1 mg in identical (monozygotic) male twins with MPHL was completed (Stough et al., 2002). Despite the small sample size in this study, the results demonstrated statistically significant benefits for the twin pairs treated with drug compared to those treated with placebo. This intriguing study confirmed the superiority of finasteride over placebo in male twin pairs with identical genetic endowment and predisposition to male pattern alopecia.

7. Is dihydrotestosterone involved in pathogenesis of female pattern alopecia?

In contrast to the established pathophysiology of MPHL in men, the androgen-dependence of FPHL in women is less clear. In a subset of women with scalp alopecia, hair loss may be associated with cutaneous signs of androgen excess, including hirsutism and acne, as well as systemic features of virilization, such as menstrual irregularities and infertility (Futterweit et al., 1988). A male pattern of hair thinning is often observed in these women (e.g., deep bitemporal recession) and hair loss may improve upon the initiation of antiandrogen therapy (Cuscan et al., 1994; O'Driscoll et al., 1994), providing evidence of the androgen-dependent nature of the condition. Women with typical FPHL, however, do not generally present with clinical symptoms of hyperandrogenism and serum testosterone

levels are usually within the normal range (Sawaya, 1998). Thus, it is unclear whether typical FPHL is due to the influence of androgens or another process.

Evidence suggesting that another process may be at work has recently come from a study in postmenopausal women with FPHL treated with finasteride (Roberts et al., 1998). In this 1-year, placebo-controlled study, treatment with finasteride 1 mg/day demonstrated no clinical benefit on scalp hair growth compared to treatment with placebo. Histopathologic evaluation of scalp biopsies confirmed that finasteride treatment produced no benefit on scalp hair in these women (Whiting et al., 1999). Because finasteride treatment produced significant reductions in the serum 5α-reduced androgen metabolites DHT and 3α-androstanediol glucuronide, the observed absence of any clinical or histologic effect of finasteride in these patients supports that factors other than DHT may be involved in the pathogenesis of FPHL in women. Further studies are needed to identify the underlying pathophysiology of common FPHL in women. In addition, future studies may demonstrate an effect of finasteride on hair loss in postmenopausal women with hyperandrogenemia and signs of androgen excess (e.g. hirsutism, acne). Finasteride use in premenopausal women who are or may potentially be pregnant is contraindicated due to the potential risk of undervirilization of a male fetus.

8. Other 5α-reductase inhibitors

Recently, limited results from clinical studies with the non-selective 5αR inhibitor dutasteride (GlaxoSmithKline) have been released. These studies, conducted in men only, demonstrated that inhibition of both isoenzymes of 5αR by dutasteride reduced scalp DHT in balding men to a greater extent than inhibition of type 2 5αR alone with finasteride. However, studies with 5αR inhibitors in an animal model of AGA, the stumptail macaque, failed to demonstrate benefit with the type 1-selective 5αR inhibitor MK-386, in contrast to the beneficial effects observed in this species with finasteride (Rhodes et al., 1994, 1995). Further studies are needed to demonstrate whether dual inhibition of 5αR is a safe and effective treatment for patients with hair loss.

9. Conclusion

Observations in eunuchs and in subjects with 5αR deficiency led to the hypothesis that androgens and, in particular, DHT were causative in the etiology of common baldness in men. The development of inhibitors of 5αR has significantly advanced our understanding of the role of androgens in men and women with hair loss. The effects of finasteride in the treatment of men with MPHL and postmenopausal women with FPHL have been documented in controlled clinical trials. While the benefit observed in men treated with finasteride supports the hypothesis that DHT is a key mediator of male pattern alopecia, inhibition of type 2 5αR was not effective in postmenopausal women with female pattern alopecia. These findings, combined with the disparate phenotypes of scalp hair loss between men and women, suggest that the pathophysiology of FPHL in women differs from that of MPHL in men. Clinical trials with non-selective inhibitors of 5αR or, more likely, studies elucidating the molecular mechanisms underlying androgen action at the level of the hair follicle, may shed further light on the biologic processes underlying common forms of hair loss in men and women.

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