Change in Hair Growth-related Gene Expression Profile in Human Isolated Hair Follicles Induced by 5-alpha Reductase Inhibitors, Dutasteride and Finasteride, in the Presence of Testosterone

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Abstract

Objective: 5-α reductase (5AR) subtypes I and II are suggested to be involved in the development of androgenetic alopecia (AGA); however, the involvement of type I 5AR in the pathogenesis of AGA and downstream molecular events following androgen receptor inhibition is still poorly understood. We investigated the changes in gene expression levels of growth factors and related molecules responsible for hair growth, such as enzymes and transcription factors, using the bulbar portions of plucked human hair follicles, and evaluated the involvement of type I 5AR in human hair growth.

Methods: Anagen hairs were plucked from male donors with AGA and cultured in medium containing dihydrotestosterone (DHT) or testosterone in the presence or absence of the 5AR inhibitors, dutasteride or finasteride. Total RNA extracted from the bulbar portions of hair follicles was subjected to quantitative reverse transcriptase polymerase chain reaction analysis to assess gene expression levels of growth factors and other related molecules.

Results: DHT stimulation resulted in a trend to decrease the expression of genes encoding fibroblast growth factor 7 (FGF7; p=0.52), insulin-like growth factor 1 (IGF1; p=0.85) and WNT family member 5A (WNT5a; p=0.08). Subsequently, testosterone stimulation led to decreased expression of genes encoding FGF7 (p=0.53), IGF1 (p=0.93) and WNT5a (p=0.51), which was reversed by dutasteride or finasteride treatment.

Conclusion: Among the assessed growth factors and other molecules related to hair growth, the expression levels of FGF7, IGF1 and WNT5a were reversed by 5AR inhibitors under testosterone stimulation. Our data suggest this assay may be useful to deeper dissect the effect of 5AR on human hair follicles and supports the previously unreported involvement of type I 5AR in hair growth.

Keywords: Androgenetic Alopecia; Dutasteride; FGF7; Finasteride; IGF1; Testosterone; WNT5a

Introduction

Dihydrotestosterone (DHT) plays a key role in the pathogenesis of male androgenetic alopecia (AGA) and is converted from the androgen, testosterone, by the enzyme 5-α reductase (5AR). DHT binds to androgen receptors (AR) in the hair follicle, which causes shortening of the anagen or growing phase of the hair cycle and leads to miniaturization of the hair follicles [1]. Over time, large terminal hairs are lost and progressively replaced by thin, short, villus-like hairs, resulting in a characteristic pattern of baldness [1,2].

Oral treatment with 5AR inhibitors (5ARIs: dutasteride and finasteride) is used in patients with male AGA and is recommended as the first-line treatment for AGA in the Japanese guidelines for the treatment of male AGA and female pattern hair loss (FPHL) [3]. Although these agents inhibit the conversion of testosterone to DHT, their mechanisms of action are different: finasteride specifically inhibits type II 5AR, but dutasteride inhibits both type I and type II 5AR [4,5]. Consequently, the superiority of dutasteride 0.5 mg to finasteride 1 mg on the change in hair count and hair width has been demonstrated in a global Phase III clinical trial [6] and documented in a review article [7].

Despite this, it is unclear whether type I 5AR is one of the enzymes driving the process of hair loss. Moreover, the downstream molecular events following 5AR inhibition are also poorly understood. Therefore, further in-depth molecular analyses are thought to be necessary to clarify the extent of the contribution of type I 5AR to hair growth.

In this study, we investigated the changes in gene expression of growth factors and other related molecules responsible for hair growth using the bulbar portions of hair follicles (BPHF) isolated from plucked human hair and evaluated the involvement of type I 5AR in human hair growth.

Materials and Methods

Ethics and informed consent

This study was approved by the Manchester Consumer Healthcare

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Hair follicle samples, cell culture and ribonucleic acid (RNA) isolation

Anagen hair follicles were plucked from the frontal, parietal and frontal/temporal area of 5 healthy male donors, with varying degrees of AGA (Norwood-Hamilton classification ranging from score 2A to 7). Plucked hair follicles were cultured in Dulbecco’s Modified Eagle’s Medium containing proprietary growth media, L-glutamine 200 nM (Sigma Aldrich, Gillingham, UK; Cat: G7513) and penicillin streptomycin (Sigma Aldrich, Cat: P0781), in the presence of DHT or testosterone in 0.1% (v/v) dimethyl sulfoxide (DMSO) or DMSO vehicle only. Hair follicles were incubated at 37°C in a 5% CO2 atmosphere for 24 hours with and without 5ARIs (dutasteride or finasteride) in the presence of testosterone as previously described with modification [8]. Post-culture, anagen hairs were visually assessed for dermal papilla cells (DPCs) and suitable candidates were chosen for lysis and RNA extraction.

Total RNA was extracted from DPCs using the Invitrogen RNAeasy total RNA isolation kit (Fisher Scientific, Loughborough, UK; Cat: 10596935). Human fibroblasts derived from skin samples (human abdominal tissue sourced from Tissue Solutions, Glasgow, UK) were used as controls.

Quantification of gene expression

For quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) analysis, RNA was reverse transcribed into complementary deoxyribonucleic acid (cDNA) as a template for qRT-PCR. PCR was conducted as follows: hot start at 95°C for 1 minute; denaturation at 96°C for 5 seconds and annealing and extension at 60°C by 3 cycles; additional extension at 60°C for 3 minutes and 60°C to 95°C for 3 seconds by 1 cycle. The list of primers is shown in Table 1 with transcription termination factor 1 (TTF1) and cyclin K (CCNK) and RNA polymerase II subunit J (POL2J) selected as housekeeping genes.

Growth factors and other related molecules in hair growth

The growth factors and other related molecules involved in hair growth that were assessed in this 3-step assay (Step I, II and III) are listed in Table 1: fibroblast growth factor 7 (FGF7), secreted by cells in the dermal papilla plays a role in stimulating hair matrix cell proliferation and hair growth [9]; insulin-like growth factor 1 (IGF1), promotes maintenance of anagen phase and stimulation of hair growth [10]; WNT family member 5a (WNT5a), mediates some of the effects of Sonic hedgehog in hair follicle morphogenesis and is capable of regulating proliferation [11,12], which have been reported to be greatly involved in hair growth, were the focus. Other related growth factors for hair growth were also analyzed such as: vascular endothelial growth factor A (VEGFA), responsible for maintaining proper vasculature around the hair follicle during the anagen growth phase [13] and platelet-derived growth factor A (PDGFA), stimulating morphogenesis of new capillaries in anagen [14]. Related surrogate markers were also analyzed such as: lymphoid enhancer binding factor 1 (Lef1) [15], in hair follicle organogenesis; bone morphogenetic protein 4 (BMP4), found in the hair placode, i.e. in the sites of Left1/b-catenin expression [16], Noggin, driving hair follicle morphogenesis and an antagonist for BMP4 [17,18], and WNT inhibitory factor 1 (Wif1), an antagonist for WNT family [19,20].

Table 1: List of assessed genes (X: assessed; -: not assessed).

<table>
<thead>
<tr>
<th>Genes</th>
<th>Full Name of Gene</th>
<th>Gene Accession No. (Reference sequence)</th>
<th>Forward Primer</th>
<th>Reverse Primer</th>
<th>Step I</th>
<th>Step II</th>
<th>Step III</th>
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<td>IGF1</td>
<td>insulin-like growth factor 1</td>
<td>NM_00111283.N</td>
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<td>VEGFA</td>
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<td>WNT5a</td>
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<td>NM_003392.N</td>
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<td>CACATCAGCCAGTGTTAC</td>
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<tr>
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<td>GCAGACTGCCTGCTCA</td>
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<td>AR</td>
<td>androgen receptor</td>
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<td>NM_002607.5</td>
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<td>GTGACTGCGGAGAATGCTGAA</td>
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<tr>
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<td>Wnt</td>
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<td>CCNK</td>
<td>cyclin K</td>
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Figure 1: Study design.
Study design

This study was conducted sequentially in 3 steps (Figure 1):

**Step I:** The changes in gene expression levels of hair growth factors (FGF7, IGF1 and WNT5a) and relevant factors were evaluated using human BPHF in the presence of DHT 1.5, 3, or 15 nM (or DMSO as a control). The concentrations of DHT used were decided based on the results of a Phase II clinical trial of dutasteride in patients with AGA [21]. During the Phase II study, the serum DHT concentration at baseline ranged from 371 pg/mL to 482 pg/mL, which equates to approximately 1.5 nM. Therefore, the starting concentration of DHT in this study was 1.5 nM, with high concentrations of 3 nM and 15 nM also investigated.

**Step II:** The changes in gene expression levels of a panel of hair growth factors were investigated in isolated human BPHF following stimulation with testosterone at a concentration of 3 nM, 10 nM or 30 nM (or DMSO as a control). The testosterone concentrations were decided based on the results of the Phase II clinical trial [21], as well as Step 1. In the Phase II study, the range of serum concentrations of testosterone at baseline was around 4.5 ng/mL, which is approximately 15 nM. In addition, 3 nM DHT was suggested to be an optimal concentration in Step I and taking into consideration the ten-fold higher potency of DHT than that of testosterone, the submaximal concentration of testosterone was speculated to be 30 nM.

**Step III:** The effects of dutasteride and finasteride on changes in gene expression levels of hair growth-related factors following testosterone stimulation (10 nM as determined in Step II) were assessed in human BPHF. The concentrations of dutasteride were 0.3, 0.03 and 0.003 nM, and the concentrations of finasteride were 1.5, 0.15 and 0.015 nM, based on the results of a Phase II/III clinical trial [6]. In the previous study, the range of concentrations for 0.5 mg dutasteride and 1.0 mg finasteride in therapeutic plasma steady-state were around 40 ng/mL (76 nM), 9 ng/mL (24 nM), respectively, which after correcting for protein binding equates to 0.2 ng/mL (0.379 nM) and 0.63 ng/mL (1.69 nM), respectively.

**Statistical analysis**

Data were analyzed by normalizing targets to the geometric mean of two
Results

Changes in gene expression level following DHT stimulation and determination of the optimal concentration of DHT (Step I)

DHT has been reported to change hair growth factor gene expression levels [22]. To confirm if both type I and II 5AR are expressed in BPHF, and if DHT exhibits bioactivities analogous to those observed in vivo in BPHF culture, the gene expression levels of hair growth-related factors, including type I and II 5AR, and changes in expression levels by DHT were evaluated.

Both type I and II 5AR were expressed in BPHF because of detection of steroid 5AR 1 and 2 (SRD5A1 and SRD5A2) (Figure 2a). Also, up to 3 nM, DHT stimulation showed a trend to decrease gene expression levels of FGF7 (p=0.52), IGF1 (p=0.85) and WNT5a (p=0.08) (Figure 2b). However, 15 nM DHT stimulation did not show consistent changes in gene expression levels in all the factors, except for AR and VEGFA. Therefore, the optimal concentration of DHT in this assay system was determined to be 3 nM; thus, 3 nM DHT was used as the base-concentration for downstream analyses (Step II).

Changes in gene expression levels following testosterone stimulation and determination of the optimal concentration of testosterone (Step II)

As DHT is converted from testosterone by 5AR in physiological conditions in human vivo, we evaluated if this assay system using testosterone mimics the physiological condition. As we expected to see changes in gene expression not only in the three factors (FGF7, IGF1 and WNT5a) observed in Step I, but also in other related factors, additional factors (VEGFA, Lef1, BMP4, PDGFA, Noggin and Wif1) were assessed in this step.

Testosterone stimulation of BPHF showed a trend to decrease the gene expression levels of three hair growth factors (FGF7; p=0.53, IGF1; p=0.93 and WNT5a; p=0.51) (Figure 3a). Additionally, Lef1 and BMP4 showed similar changes to the above three factors (FGF7, IGF1...
and WNT5a) in gene expression levels, whilst Noggin and Wif1 showed opposite changes to these three factors (Figure 3b). Although the gene expression of VEGFA was concentration-dependently increased alongside that of testosterone, this change was opposite to that observed in Step I. Similar to that observed in Step I, the maximal concentration of testosterone (30 nM) was considered to cause saturation in WNT5a, PDGFA and Noggin; therefore, 10 nM was determined as the optimal testosterone concentration to use in Step III.

Effect of 5ARIs on changes in gene expression levels in the presence of testosterone (Step III)

Theoretically, dutasteride and/or finasteride in this assay system were considered to show inhibitory effects on the observed changes in gene expression level of the hair growth factors under testosterone stimulation. Moreover, we expected that the inhibitory potency of dutasteride and finasteride would be reflected in the observed gene expression levels. Thus, the effects of dutasteride and finasteride on changes in gene expression levels of a panel of hair growth factors, under stimulation with testosterone at an optimal concentration (10 nM), as determined in Step II, were investigated.

Gene expression levels of FGF7, IGF1 and WNT5a with dutasteride or finasteride under testosterone stimulation showed a consistent trend of re-increasing (Figure 4a). The fold change (mean ± standard error of the mean) in FGF7 expression compared with the DMSO control ranged from 1.00 ± 0.25 to 1.53 ± 10.04 (p=0.10) with finasteride and 0.93 ± 0.36 to 1.22 ± 0.10 (p=0.23) with dutasteride. Similarly, IGF1 expression ranged from 0.56 ± 0.78 to 4.34 ± 2.71 (p=0.72) under finasteride treatment and 1.70 ± 0.78 to 2.73 ± 1.24 (p=0.61) under dutasteride treatment. WNT5a expression ranged from 1.03 ± 0.99 to 1.14 ± 0.10 (p=0.26) or 1.08 ± 0.25 to 1.21 ± 0.20 (p=0.65) under finasteride or dutasteride treatment, respectively.

The expression of Noggin and Wif1 showed a trend of increasing in the presence of testosterone stimulation (Figure 3b). Noggin is a known inhibitor of BMP4 [17]; therefore, the results observed were consistent with the expression of BMP4 decreasing in a concentration dependent fashion. Similarly, the results for Wif1 (a WNT antagonist) [20,23] were consistent with those of WNT5a as it showed a trend for reduced expression (Figure 4b).

The gene expression of PDGFA showed a consistent trend toward
decreasing with increasing 5ARI concentrations (Figure 4b). The changes in gene expression level of VEGFA and LeF1 were shown to be inconsistent (Figure 4b).

In addition, the expression of hair growth factors under testosterone stimulation was evaluated in isolated human fibroblasts to confirm whether the observed changes in gene expression levels were induced specifically in BPHF. No genes were shown to decrease under testosterone stimulation in human fibroblasts, thus showing that the effects on gene expression were specific to BPHF.

Discussion

By utilizing the BPHF isolated from plucked human hair in this assay system, we investigated why dutasteride is more effective at promoting human hair growth compared with finasteride, which was demonstrated in a clinical trial [6]. We also evaluated the involvement of type I 5AR in human hair growth.

Through Steps I, II and III, this assay system using plucked human hairs is considered to detect changes in gene expression levels of growth factors and other related molecules responsible for hair growth. By measuring changes in gene expression levels of targeted genes (e.g. FGF7, IGF1 and WNT5a, which are known to be important in hair growth), new candidates of 5ARIs and medicines may be evaluated at the gene level; however, the assay system needs to be further developed.

In Step I, stimulation of BPHF with 15 nM DHT was considered to result in saturation of the trend to decrease gene expression in three factors, FGF7, IGF1 and WNT5a, possibly due to over concentration of DHT and/or DHT-induced down-regulation of 5ARs in the cells. Furthermore, changes in gene expression levels of other related molecules (VEGFA, LeF1 and PDGFA) were shown to be inconsistent in all steps. This could be due to the use of BPHF with other components, not purely isolated DPCs.

Of note, dutasteride and finasteride showed the trend to cancel suppressive effects of testosterone on hair-related gene expression presumably in DPCs in Step III, as the expression levels of targeted genes (FGF7, IGF1 and WNT5a) were increased. Taking into consideration the inhibitory potency of dutasteride and finasteride, there was a trend toward differing changes in gene expression of the investigated genes and factors between the two 5ARIs. The effect of finasteride on the expression of FGF7, IGF1 and WNT5a plateaued at the middle concentration evaluated (0.15 nM), but the effect of dutasteride was linear to the highest concentration tested (0.3 nM), although these findings were not statistically significant. This observation suggests that dutasteride may have a stronger inhibitory potency to increase growth factor expression than finasteride, possibly due to the inhibition of type I 5AR by dutasteride, but not finasteride. Furthermore, our results suggest that type I 5AR may play an important role in hair growth, as well as type II 5AR [9,10]. Furthermore, expression of WNT5a in developing hair follicles requires Sonic hedgehog. This result suggests that WNT5a may mediate some of the effects of Sonic hedgehog in hair follicle morphogenesis, a hypothesis supported by the fact that both WNT5a and Sonic hedgehog are capable of regulating proliferation [11]. Noggin is a known inhibitor of BMP4 [17]; therefore, results were consistent with the expression of BMP4 decreasing in a concentration dependent fashion. Similarly, the results for Wg1, a WNT antagonist [20,23], were consistent with those of WNT5a, showing a trend toward differing expression. Thus, FGF7, IGF1 and WNT5a were confirmed again as key factors in hair growth in the study.

As with other in vitro/ex vivo studies, potential limitations of this study include the fact that any changes in gene expression could not be verified to lead to corresponding changes in protein levels. Although this study focused on changes in gene expression levels, the effect on protein expression should also be assessed using an appropriate method, such as an enzyme-linked immunosorbent assay. Furthermore, the concentrations of DHT converted from testosterone in the culture medium were not assessed in Steps II and III. Testosterone induced changes in gene expression of several genes, and testosterone conversion to DHT was inhibited by 5ARs in the BPHF; however, a more precise investigation may be necessary, such as determination of DHT concentration in the medium. Another limitation of this preliminary study was the small sample number. Studies with a larger sample size (e.g. >35 subjects) should be considered in the future. For this reason, interpretation of the results for testosterone stimulation alone and in the presence of dutasteride/finasteride should be carefully considered. In addition, hair growth ex vivo culture was not assessed directly, because of the study design; incubation time of 24 hours is too short and difficult to assess hair shaft length, hair width etc. Hence, we could not reach the changes in the gene expression that would lead to changes in the efficacy endpoints such as hair shaft lengths, hair width, hair count etc. Finally, analyses and interpretation of data may be difficult possibly due to the use of BPHF instead of pure DPCs; therefore, assays using pure DPCs are expected to show more clear-cut results and provide more in-depth interpretation.

Conclusion

Our study indicates that dutasteride and finasteride are potent modulators of the expression of genes encoding hair growth factors and other molecules potentially related to hair growth. In terms of key important genes in hair growth, such as FGF7, IGF1 and WNT5a, this study showed that dutasteride may be more potent than finasteride in modulating gene expression levels. This study provides supporting evidence that type I 5AR may be an enzyme involved in hair growth, in addition to type II 5AR. The results of this study provide indications of an in-depth downstream mechanism of action by 5ARs and it is expected to further clarify the importance of the function of type I 5AR.

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Conflicts of Interest

TH, ZL, MY and GO are employees of GlaxoSmithKline. TM, CB and EH are employees of Epistem.

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References


