Prostanoids and Hair Follicles: Implications for Therapy of Hair Disorders

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Prostanoids, including prostaglandins (PGs) and thromboxane A2 (TXA2), are a family of lipid-derived autocoids that modulate many physiological systems and pathological contexts. Prostanoids are generated by sequential metabolism of arachidonic acid, catalysed by cyclo-oxygenase, to PGH2, which is then converted to PGD2, PGE2, PGF2α, PGI2, and TXA2, catalysed by their specific synthases. Recent evidence suggests that prostanoids play a role in regulating hair growth. The PGF2α analogue is Food and Drug Administration-approved in the US and routinely used to enhance the growth of human eyelashes. PGE2 is reported to protect from radiation-induced hair loss in mice. Conversely, PGD2 inhibits hair growth. This paper reviews the metabolism of prostanoids and the expression pattern of prostanoid receptors in hair follicles, focussing on their different and opposing effects on hair growth and the underlying mechanisms. This has potential clinical relevance in the treatment and prevention of hair disorders.

Key words: prostanoid; prostaglandin receptor; PGF2α analogue; hair follicle.

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Prostaglandins (PGs) and thromboxane A2 (TXA2) are termed prostanoids and are derived from arachidonic acid and other long-chain polyunsaturated fatty acids (1). The biosynthesis of prostanoids begins with the release of arachidonic acid from the plasma membrane of cells by phospholipases (PLAs), following metabolism via the sequential actions of cyclo-oxygenase (COX) and respective synthases. Prostanoids modulate many physiological systems, including the immune, respiratory, gastrointestinal, cardiovascular, and genitourinary systems (1, 2).

Research on prostanoids has focused on inflammation and inflammatory responses, and the relationship between prostanoids and hair follicles has been investigated largely through adverse events and case reports (3, 4). This review discusses the biosynthesis of prostanoids and their metabolism in hair follicles, with particular regard to advances in research into prostanoids and hair follicle growth, hair follicle cycle, and hair disorders.

PROSTANOID METABOLISM

There are 2 main COX isoforms, COX-1 and COX-2, both of which can transform arachidonic acid into PGH2. COX-1 is constitutively expressed, while COX-2 is induced by mitogenic and pro-inflammatory stimuli. PGH2 is then transformed into different PGs and TXA2, catalysed by different synthases. The mainly bioactive prostanoids generated in vivo include PGE2, PGI2, PGD2, PGF2α, and TXA2. TXA2 is characterized as modulating haemodynamics and cardiovascular functions; therefore this review focusses on other PGs. Prostanoids act as autocrine/paracrine local hormones through specific G-protein-coupled receptors. The 5 types of prostanoids, PGE2, PGI2, PGD2, PGF2α, and TXA2, bind to PGE2 receptors (EP1, EP2, EP3, EP4), PGI2 receptor (IP), PGD2 receptors (DP1, DP2), PGF2α receptor (FP), and thromboxane A2 receptor (TP) respectively (Fig. 1). Different prostanoids have different, or even opposing, properties, possibly due to the fact that they bind to different receptors and
have different signalling pathways induction (Table 1) (5). This review focuses mainly on PGD₂ and PGF₂α, which are more closely related to hair growth.

There are 2 PGD₂ synthases, lipocalin PGDS (L-PGDS) and haematopoietic PGDS (H-PGDS). These differ biochemically with respect to features such as sequence, structure, cellular localization and tissue distribution (6). PGD₂ can bind and activate 2 distinct receptors, DP1 and DP2 (2). DP1 triggers Gs-type G-protein-coupled adenylate cyclase, which increases intracellular cAMP and calcium flux. DP2 triggers Gi-type G protein, which leads to inhibition of cAMP and calcium flux. PGD₂ can act as either a pro- or anti-inflammatory mediator, depending on the disease process and aetiology. The expression pattern of L-PGDS/H-PGDS and DP1/DP2 may account for different signalling pathway activation post-PGD₂ production. Unlike PGD₂, PGF₂α binds to a single receptor, FP. Activation of FP leads to Gaq-type G protein-mediated IP₃ generation and increased intracellular calcium flux (2). The FP receptor can also couple to the small G-protein Rho via a Gq-independent mechanism. However, in high concentrations, PGF₂α can also activate EP2. High concentration PGE₁ can activate FP and both the cross-activation of EP and FP can lead to COX-2 expression (1). Cross-talk between the FP and EGF receptor signalling and the β-catenin pathway has also been reported. The effects of prostanooids on these G-protein-coupled signalling pathways may also change as a function of ligand concentration or structure. These characteristics might explain their synergistic and/or antagonistic effects in many physiological systems and a broad array of diseases (Fig. 1).

### HAIR FOLLICLE BIOLOGY

Anatomically, the hair follicle is an intricate mini-organ comprising epithelial and mesenchymal cells. The structure of hair follicles from outside to inside includes a fibrous connective tissue sheath, an outer root sheath, an inner root sheath, and the hair shaft (7). Together with the sebaceous gland and the arrector pili muscle, the hair follicle is part of the pilosebaceous unit. A rich blood supply flows to the hair follicles, and hair follicles are also richly innervated. In general, hair follicles can be divided into a permanent upper part and a transient lower cycling part, based on their differences during the hair cycle and their biological characteristics (8). The hair follicle cycle consists of stages of hair growth (anagen), follicle regression (catagen), rest (telogen), and hair shedding (exogen) (7, 9). The hair matrix and proximal outer root sheath (transient lower part) are degenerated by apoptosis during catagen. At the onset of anagen, bulge stem cells in the permanent part transiently produce their descendants, which actively proliferate and migrate to the lower part to regenerate the lower cycling part. The hair cycle in humans is asynchronous, which differs from many other mammals with synchronous hair cycles. Under physiological conditions, approximately 84% of the human scalp hair follicles are in anagen, 2% in catagen, and 14% in telogen, and 70–100 hairs are shed daily. The duration of the entire hair cycle depends on the location and type of hair follicle. The final length of hairs is proportional to the duration of anagen. For example, human eyebrow hair follicles and eyelash hair follicles are short because the anagen phase of hair follicles of eyebrow is only 2–4 weeks and the anagen phase of eyelash hair follicles is 1–4 months, while scalp follicles grow long because they stay in anagen for 2–6 years (10, 11). Except for rare congenital hair disorders and wound-induced “scarring” alopecia, most patients’ hair disorders are related to aberrations in hair follicle cycling.

### PROSTANOIDS AND PROSTANOID RECEPTORS IN HAIR FOLLICLES

In a mouse telogen skin model, COX-1 was the major isoform expressed in keratinocytes of the interfollicular epidermis and the upper part of the hair follicle, whereas COX-2 protein was barely detectable (12). Müller-Decker et al. (13) demonstrated that COX isozymes were spatiotemporally expressed during morphogenesis of mouse dorsal skin. COX-1 was detected in spinous and granular keratinocytes of the suprabasal compartment at E15–E18, and this pattern of expression was detected in skin through day 28 after birth, as well as in the skin of 7-week-old mice. Dendritic cells located interfollicularly and in the distal portion of the hair follicle of neonatal and adult skin were also COX-1 positive, which might indicate a role of COX-1 in the skin immune system. COX-2

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Table I. Expression pattern and signal transduction of prostaglandin (PG) receptors

<table>
<thead>
<tr>
<th>Class</th>
<th>Subtype</th>
<th>Expression pattern</th>
<th>G-protein-coupled</th>
<th>Second messenger</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGD₂</td>
<td>DP1</td>
<td>Basal layer of epidermis (+/-) hair follicle ORS (+)</td>
<td>Gs</td>
<td>cAMP, Ca²⁺¹</td>
</tr>
<tr>
<td></td>
<td>DP2</td>
<td>All epithelial compartments of epidermis and hair follicle (+/-)</td>
<td>Gi</td>
<td>cAMP, Ca²⁺¹</td>
</tr>
<tr>
<td>PGE₁</td>
<td>EP1</td>
<td>Basal cells of epidermis (+), hair follicles (+), DP (+)</td>
<td>Gq</td>
<td>IP₃/DAG/Ca²⁺¹</td>
</tr>
<tr>
<td></td>
<td>EP2</td>
<td>Epidermis (+, perinuclear expression), hair follicles (+), DP (+)</td>
<td>Gs</td>
<td>cAMP¹</td>
</tr>
<tr>
<td></td>
<td>EP3</td>
<td>Epidermis (+, nuclear expression), hair follicles (+), DP (+)</td>
<td>Gi, G12</td>
<td>cAMP¹, Ca²⁺¹, Rho</td>
</tr>
<tr>
<td></td>
<td>EP4</td>
<td>Epidermis (+, cytoplasmic expression), hair follicles (+), DP (+/-)</td>
<td>Gs</td>
<td>cAMP¹</td>
</tr>
<tr>
<td></td>
<td>PGF₁</td>
<td>IP</td>
<td>hair shaft cuticle cells (+), epidermis (+/-)</td>
<td>Gs</td>
</tr>
<tr>
<td></td>
<td>PGF₂α</td>
<td>FP</td>
<td>Epidermis (-), most hair compartments (+)</td>
<td>Gq</td>
</tr>
</tbody>
</table>

DP: dermal papilla; IRS: inner root sheath; ORS: outer root sheath.
appeared in all cells of elongated hair germs and hair pegs during hair morphogenesis. During the gradual transition of early stage hair follicles into fully differentiated follicles after birth, COX-2 expression became restricted to basal outer root sheath (ORS) and sebaceous gland cells (12). When follicles entered catagen, COX-2 expression declined, and was barely detectable in telogen follicles (12). As the key reaction in PG biosynthesis, COX-1 and COX-2 are spatiotemporally expressed during hair follicle morphogenesis and hair follicle cycling, which may contribute to PG production and hair follicle biology.

Several studies on prostanoid metabolism and prostanoid receptor distribution in human hair follicles have been reported (Table I). Colombe et al. (13) investigated the expression profile of key enzymes of PG metabolism in human hair follicles. Their experiments revealed that human hair follicles expressed mPGES-1, mPGES-2 and cPGES, which catalyse PGH\(_2\) to PGE\(_3\), as well as AKR1C3/PGFS, which converts PGH\(_2\) to PGF\(_{2\alpha}\) (13). These observations support the concept that PGs are involved in hair growth and differentiation control. Garza et al. (14) measured the expression level of Ptgds mRNA during hair cycles and found that Ptgds peaked in late anagen and was much higher than in telogen, similar to the expression pattern of fibroblast growth factor 5 (a known marker of catagen onset). They further discovered that PGD2 peaked after the apex of Ptgds expression. They claimed that Ptgds was first expressed in late anagen and PGD2 was produced via Ptgds during catagen, indicating that the PGD\(_2\) pathway directly induced the apoptotic catagen stage. Using immunohistochemistry techniques on mouse skin tissue, Ptgds was evident in late anagen in the keratinocytes of the ORS below the arrector pili muscle. In human hair follicles, a similar presence of PTGDS in the non-permanent region of hair follicles has been found (14).

All of the prostanoid receptors have been reported as present in hair follicles (5). Most of these receptors have shown a wide spectrum of expression in cultured cells and whole hair follicles (Table SI\(^1\)). The expression of EP\(_2\), EP\(_3\), EP\(_4\), DP\(_1\), and TP and, to a lesser extent, EP\(_1\), involved several hair follicle compartments (5). Conversely, IP and DP\(_1\) were more specifically expressed in the hair cuticle layer and ORS basal layer, respectively (5). FP expression was restricted to the ORS companion layer and dermal papilla (5). Nesher et al. performed an immunohistological study of human eyelids, finding that FP was located predominantly in the inner root sheath of the bulb and stem of eyelashes and expressed only in eyelashes in the anagen phase (15). Therefore, the expression pattern of different prostanoid receptors may differ in different tissues or species. Although the exact functional significance of the expression of these prostanoid receptors remains unclear, it does explain some biological effects of some PGs, such as how FP expression in dermal papilla is related to the effect of PGF\(_{2\alpha}\) on hair growth. All these observations of prostanoids and prostanoid receptors support the idea that prostanoids are involved in hair biology.

### PROSTAGLANDIN-INDUCED HAIR GROWTH

The potential role of PGs in the treatment of alopecia was first noted in the observation that eyelashes and eyebrows grew longer as a side effect following topical application of PG analogues in glaucoma treatment. Latanoprost was first documented as a hair-growth stimulant by Johnstone in 1997 (3). In 43 patients receiving unilateral topical latanoprost, hypertrichosis involved the ipsilateral terminal eyelashes and regional intermediate hairs of the upper and lower eyelid, as well as vellus hair of the lower eyelid skin. Increased hair numbers, length, thickness, curvature, and pigmentation were observed in the latanoprost-treated eye. Recently, a placebo-controlled trial in men with mild androgenetic alopecia (AGA) showed that the application of 0.1% latanoprost significantly increased hair density and pigmentation (16). Sixteen men with AGA (Hamilton-Norwood patterns of baldness II–III) were treated with 0.1% latanoprost and placebo on two mini-zones of the scalp. Compared with the baseline and placebo-treated sites, the latanoprost-treated sites showed increased hair density. Coronel-Pérez et al. conducted a survey of subjects with alopecia areata (AA) universalis treated with injections of triamcinolone acetonide and latanoprost 0.005% ophthalmic solution in their eyelid margins, and total or moderate responses were reported by 45% of subjects (17). However, Faghihi et al. and Ross EK et al. reported no efficacy of topical latanoprost in the treatment of eyelash and eyebrow AA (18, 19).

Bimatoprost is the only Food and Drug Administration (FDA) approved PGF\(_{2\alpha}\) analogue for the treatment of eyelash hypotrichosis (Fig. 1, Table SI\(^1\)) (20–22). The efficacy and safety of bimatoprost in the treatment of eyelash hypotrichosis has been well documented, with clinical ratings, digital image analysis, and patient-reported measures of satisfaction (Table SI\(^1\)) (23–26). A clinical study showed that, compared with latanoprost, the application of ophthalmic bimatoprost solution (0.03%) resulted in a higher occurrence of eyelash growth. A recent retrospective review of 585 subjects treated with 0.03% bimatoprost for eyelash hypotrichosis revealed a patient satisfaction level of 92.5%, and long-term use for at least 12 months was safe (25). Many clinical trials and observations have also reported the use of bimatoprost in other hair disorders, including thinning of the eyebrows, eyebrow hypotrichosis, and chemotherapyy-induced hypotrichosis (Table SI\(^1\)). One study showed that bimatoprost was equally efficacious as minoxidil in enhancement of eyebrow thickness, with fewer side-
effects (27). A multicentre, double-blinded, randomized, parallel-group study showed that daily treatment with bimatoprost ophthalmic solution 0.03% for 1 year was effective and well tolerated in patients with idiopathic and chemotherapy-induced eyelash hypotrichosis (28).

The efficacy and safety of topical bimatoprost for alopecia areata (AA) has been controversial or negative (29–31). A 1-year retrospective study indicated that 43.24% of patients with AA universalis achieved an acceptable cosmetic response with 0.03% bimatoprost (30). However, reports indicated no efficacy of bimatoprost in the treatment of AA. Roseborough et al. (32) enrolled 11 eyelash AA patients in a 16-week, randomized, investigator-masked, controlled study, which showed no significant changes in any patients. Borchert et al. (33) enrolled 71 adolescents with chemotherapy- or AA-induced eyelash hypotrichosis and healthy controls in a multicentre, randomized, double-masked, parallel-group study. Significant treatment benefits with bimatoprost vs. vehicle were evident among the healthy adolescents, but not in the post-chemotherapy or AA subgroups. Some authors have questioned whether these treatment failures were due to inadequate penetration of hair follicles without eyelashes, irreparable damage of follicle stem cells or too severe alopecia, among other reasons (31). However, these “positive” studies were uncontrolled or poorly controlled, and the controlled studies have been “negative”. Therefore, more studies with a larger sample size, longer study duration, and higher concentration of medication are suggested to confirm whether PGF\textsubscript{2α} analogues are effective in treatment of AA. The application of bimatoprost in the treatment of AGA also needs further study. Emer et al. (34) reported a case of female-pattern androgenetic alopecia (AGA) patient who failed to respond to injected 0.03% bimatoprost solution. Numerous clinical trials on using bimatoprost in AGA are currently registered in the US National Institutes of Health Clinical Trials database (https://clinicaltrials.gov) (Table SI) and the results on efficacy and safety of bimatoprost in AGA will be reported on publication of these trial results.

Although latanoprost and bimatoprost are generally safe, patients should be informed about and monitored for local and systemic side-effects. The most common local side-effects are eye pruritus, conjunctival hyperaemia, eye irritation, dry eye symptoms, and erythema and hyperpigmentation of the eyelids (31). The association of uveitis and herpetic simplex viral infection has also been documented. Systemic side-effects include upper respiratory tract infection, headache, abnormal liver function tests, and asthenia. Although no foetal malformations have been reported, bimatoprost is classified as a Food and Drug Administration (FDA) category C medicine because of potential side-effects.

Despite the publication of many clinical reports and studies of PG-induced hair growth, the underlying mechanisms are largely obscure. The effects of bimatoprost treatment are believed to result from longer duration of anagen, increased hair bulb thickness, and increased melanogenesis (35). Mouse studies of latanoprost have suggested that telogen follicles are induced into the anagen phase within 8 days of treatment (36). In one study using a murine model, mice receiving bimatoprost 0.03% ophthalmological solution once daily for 14 days were compared with mice treated with vehicle control. Every hair follicle of each eyelid was classified into a phase of the hair cycle (37). The bimatoprost-treated group demonstrated a significantly greater proportion of anagen follicles and a decrease in telogen and late catagen follicles, suggesting that bimatoprost extends the duration of the anagen phase.

Studies have also reported other PG analogues with hypertrichosis effects, such as travoprost (38). PGE\textsubscript{2} has been shown to protect mice from radiation-induced alopecia (39). Minoxidil was the first FDA-approved topical medicine for the treatment of AGA. The effect of minoxidil on hair growth is well known. Even though potassium channel opening, leading to increased cutaneous blood flow and stimulation of dermal papilla activity, has been proposed as the mechanism of the effect of minoxidil on hair growth, its exact mechanism of action on hair growth is uncertain (40). Studies have also suggested that minoxidil enhances hair growth by increasing the production of PGE\textsubscript{2} and inhibiting prostacyclin synthesis by cultured dermal papilla cells (40, 41), further confirming the stimulating effects of PGs on hair growth.

**PROSTAGLANDIN-INHIBITED HAIR GROWTH**

That PGs stimulate hair growth has long been confirmed by evidence. However, the inhibiting effects of PGs on hair growth have not been given attention until recently.

Several COX-2 over-expression transgenic mouse models have been developed with characteristic phenotypes of hair dysregulation. Neufang et al. (42) developed a heterozygous transgenic mouse model using a bovine keratin 5 promoter to direct COX-2 expression in the basal cells of the interfollicular epidermis and the pilosebaceous unit. The constitutive overexpression of COX-2 led to delayed hair follicle morphogenesis, reduced hair follicle density, sebaceous gland hyperplasia, and profound hyperplasia in the scale epidermis of the tail with foci exhibiting signs of dysplasia (42). Bol et al. (43) generated a transgenic mouse model that overexpressed COX-2 under the control of human keratin 14 promoter, which presented with distinct alopecia. Atrophy of the skin, pyknotic nuclei, and enlargement of sebaceous glands were also observed in the K14-COX-2 transgenic mice. Administration of celecoxib (a selective COX-2 inhibitor) restored hair growth, further indicating that the alopecia was due to elevated COX-2 activity. Müller-
Decker et al. (12) described a homozygous transgenic mouse model with COX-2 overexpression under the control of keratin 5 promoter. The overexpression of COX-2 induced a precocious entry into the first catagen stage and a subsequent disturbance of the hair follicle cycle. Alopeia and sebaceous gland hyperplasia were also observed, and inhibition of transgenic COX-2 activity with the specific COX-2 inhibitor suppressed the development of alopeia (12). However, further studies on the COX-2 expression pattern and PGE₂ metabolism did not succeed in clarifying the exact relationship between PGs and inhibition of hair growth.

It was not until PGD₂ was confirmed as inhibiting hair growth in patients with AGA that researchers began to pay attention to the inhibiting effects of PGs in hair growth. Garza et al. first reported the elevation of PTGDS and PGD₂ in the bald scalp compared with the haired scalp of men with AGA (14). During normal follicle cycling in mice, Ptgs and PGD₂ levels increase immediately before the regression phase, suggesting their inhibitory effect on hair growth. Garza et al. further confirmed that PGD₂ decreased hair growth through DP2 and not through DP1. Using wound-induced hair follicle neogenesis (WIHN) as a marker of skin regeneration, they also confirmed that PGD₂ decreased hair follicle neogenesis (44). Exogenous application of PGD₂ decreased WIHN in wild-type mice and the PGD₂ receptor DP₂ null mice showed increased WIHN compared with strain-matched control mice. Recently, Zheng et al. (45) reported that DP2 antagonists reversed the hair growth inhibition mediated by PGD₂ in a dose-dependent manner by reducing PGD2-triggered apoptosis and maintaining keratinocyte proliferation. They further confirmed that topical application of PGD₂ resulted in accelerated entry into catagen in a mouse model, while DP2 antagonists extended the anagen phase. Flow cytometry analysis verified that PGD₂ decreased Ki67+ cells in the secondary hair germ population. Mantel et al. (46) reported that PGD₂ enhanced testosterone metabolism in human keratinocytes, which initially set up the connection between PGD₂ and testosterone metabolism. The role of testosterone and dihydrotestosterone as drivers of AGA is well established. Based on these results, we can conclude that exploration of the role of PGD₂ in inhibiting hair growth via the DP2 receptor and in pharmacological antagonists of DP2 is a potential approach for hair disorder prevention and treatment (Fig. 1).

CONCLUSION

Different prostanoids may have different or even opposing effects on hair follicles through different signalling pathways. Although research on the role of prostanoids and prostanoid receptors in hair follicles has been carried out, more detailed studies are needed to understand their diverse actions on hair growth and signalling profiles. Recent advances have shown that PGF₂α analogues and DP2 antagonists have therapeutic potential for hair loss. However, more research is required to clarify the efficacy, safety, and mechanisms of these prostanoids in treating hair disorders.

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