The Effect of Parathyroid Hormones on Hair Follicle Physiology: Implications for Treatment of Chemotherapy-Induced Alopecia

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Key Words

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Abstract

Parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP) influence hair follicles through paracrine and intracrine routes. There is significant evidence that PTH and PTHrP influence the proliferation and differentiation of hair follicle cells. The PTH/PTHrP receptor signalling plays an important role in the hair follicle cycle and may induce premature catagen-telogen transition. Transgenic mice with an overexpression or blockade (PTH/PTHrP receptor knockout mice) of PTHrP activity revealed impaired or increased hair growth, respectively. Some findings also suggest that PTHrP may additionally influence the hair cycle by inhibiting angiogenesis. Antagonists of the PTH/PTHrP receptor have been shown to stimulate proliferation of hair follicle cells and hair growth. A hair-stimulating effect of a PTH/PTHrP receptor antagonist applied topically to the skin has been observed in hairless mice, as well as in mice treated with cyclophosphamide. These data indicate that the PTH/PTHrP receptor may serve as a potential target for new (topical) hair growth-stimulating drugs, especially for chemotherapy-induced alopecia.

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Introduction

Hair follicles are not only hormone-dependent structures, but they can also produce a variety of hormones acting in a paracrine, autocrine or intracrine manner, therefore causing changes directly in the skin and in hair biology [1–3]. Thus, hormones produced by the skin and the hair follicles may play an important role in maintaining or dysregulating hormonal homeostasis, in general. This endocrine function of the skin and hair follicles appears to be underestimated. Already, the expression of multiple numbers of hormones and their receptors has been discovered in hair follicles [4, 5]. Hair follicles seem to be fascinating dermato-endocrinological units.

Among endocrine disorders which are important in hair biology, hyperandrogenism is best investigated [6, 7]. It has also been recently proven that thyroid abnormalities are strongly associated with hair growth [8]. There is a putative role of glucocorticosteroids and prolactin in hair biology [9, 10]. The role of parathyroid hormone (PTH) and abnormalities of parathyroid gland function in hair growth remains not well understood.

Primary hyperparathyroidism is related to an increased activation of α_1 -hydroxylase and calcitriol synthesis. It leads to phosphate absorption in the gastrointestinal tract and phosphate reabsorption in the proximal tubules of the kidneys. A rising level of phosphates activates a negative feedback mechanism in the vitamin D and PTH axis. This

results in an increased ability to eliminate calcitriol by CYP24B1 (cytochrome P 450 family 24 subfamily B, one of the genes involved in the vitamin D metabolism pathway) [11, 12]. PTH, an inhibitor of hair development, competes with calcitriol, which stimulates hair growth [13]. The final effects may vary among patients, and this must be taken into consideration when studying hair pathophysiology [14]. PTH, produced by the parathyroid gland, has been found to be expressed in the hair follicle, as well as its receptors [15]. It has been proven that PTH is another factor playing a role in the regulation of the hair growth cycle. An agonist of the receptor for PTH, the parathyroid hormone-related protein (PTHrP), is also expressed in skin and hair follicles, regulating their proliferative activity. There is a significant body of evidence suggesting the potential role of parathyroid hormone receptor (PPR) ligands. It has been proven that agonists or antagonists of PPR can inhibit/promote hair growth [16]. Despite the potent role of PTH/PTHrP in hair growth modulation, there is still a lack of studies regarding parathyroid-related disorders. Also, general mucocutaneous manifestations of PTH-related disorders seem to be underevaluated, especially in non-familial cases of parathyroid disorders.

Hair Follicle Morphology

The development of the skin with its appendages is necessary for humans to create a well-functioning skin barrier [17]. The human pilosebaceous unit is a highly proliferating organ. This capability is crucial in understanding the role of its numerous dermato-endocrinological cross-actions [4]. The hair follicle is also a fascinating subject for molecular biologists, who find it to be a perfect model for studies. As knowledge broadens, the biology of the hair follicle seems to be more and more complicated. The follicular unit, which consists of the hair follicle, the sebaceous gland and the arrector pili muscle, is derived from epithelium and mesenchyme cell layers, which create different compartments of the hair unit with their own unique functions [18].

Hair follicle structure can be divided into two elements: a permanent superficial structure and non-permanent portion, known as the cycling region [19]. The line of that division lies below the hair follicle bulge region, so below the insertion point of the arrector pili muscle. The bulge region is in fact a part of the outer root sheath, and it has been proven to consist of stem cells [19]. A transient, cycling portion, including the hair bulb, is crucial for regenerative ability [19]. Rapid proliferation of

cells in the bulb region (adjacent to the dermal papilla) during the anagen phase causes hair shaft and inner root sheath growth [20]. In accordance with that, damage of the dermal papilla results in an inability to provoke the regrowth of hair [21]. All compartments of the hair unit, including the epithelium of the follicle's outer and inner root sheaths, the bulge area, the dermal papilla, the matrix cells containing melanocytes, the surrounding nerves, sebaceous glands, vasculature and lymphoid cells, cross-act with each other and regulate the hair growth cycle [22]. Each of these various hair follicle compartments acts as a specific location of production and/or reception of diverse hormones impacting the hair growth cycle.

Hair Growth Cycle

Humans are born with approximately 2 million follicular units, and no new hair follicles are created after birth. It has been shown that the significant regenerative ability of hair depends on the hair growth cycle phenomenon [23].

The hair growth cycle consists of three main phases: anagen (growth phase), catagen (regression phase) and telogen (resting phase) [24]. Anagen is a phase of active proliferation resulting in hair growth. Catagen is related to cessation of protein and pigment production, involution of the hair follicle and restructuring of the extracellular matrix. In the third, resting phase, called telogen, the hair follicle regresses. Recently, it has also been shown that shedding is, in fact, an active process which differs from telogen. To distinguish the shedding phase, researchers have named this process the exogen phase [25]. It has been discovered that exogen refers to a proteolytic activity in the cells of the telogen shaft base. It is also known that this is connected to a loss of desmoglein 3 [26]. Kenogen is another stage of the hair cycle which can sometimes be observed. It occurs after shedding, when the empty hair follicles of the hair shaft can be observed and before the onset of new anagen. Clinically, it evokes a lack of hair coverage after shedding, and it is seen most frequently in androgenetic alopecia patients [27].

The hair follicle cycles go from anagen to telogen continuously, but a crucial and key target in this cycle seems to be the length of the growth phase. It must be noted that the length of anagen, which is also dependent on the body site location, determines the physical appearance of hair [2, 28].

Changes in the hair growth cycle often result in alopecia. However, it may be possible to promote the anagen phase to treat hair loss disorders.

Table 1. The modulators of the hair cycle

Promoters of anagen	Inducers of premature catagen-telogen transition
<p> β-Catenin [90] Fibroblast growth factor 2 (FGF-2) [91] Fibroblast growth factor 7 (FGF-7) [92] Hepatocyte growth factor (HGF) [93] Insulin-like growth factor 1 (IGF-1) [94] Lymphoid enhancer-binding factor 1 (LEF-1) [95] Macrophage-stimulating factor (MSP) [96] Platelet-derived growth factor (PDGF) [97] Sonic hedgehog (SHH) [94] Transforming growth factor α (TGF-α) [98] Noggin (NOG) [99] Vascular endothelial growth factor (VEGF) [48] WNTs [100] </p>	<p> Brain-derived neurotrophic factor (BDNF) [101] Bone morphogenetic protein 2 (BMP-2) [102] Bone morphogenetic protein 4 (BMP-4) [102] Epidermal growth factor (EGF) [103] Fibroblast growth factor 2 (FGF-2) [104] Fibroblast growth factor 5 (FGF-5) [105] Interleukin 1 (IL-1) [106] Interleukin 6 (IL-6) [107] Interferon γ (IFN-γ) [108] Neurotrophin 3 (NT-3) [109] Oncostatin (OSM) [110] Parathyroid hormone (PTH) [16] Transforming growth factor β_1 (TGF-β_1) [111] Transforming growth factor β_2 (TGF-β_2) [112] </p>

Additionally, the longer the telogen, the greater the chance of kenogen, resulting in the clinical presentation of lack of hair [1]. Conversely, factors shortening telogen and promoting anagen will decrease the percentage of kenogen hair follicles [29]. Factors and drugs elongating/promoting anagen, as well as those reducing the duration of telogen, are the targets for researchers investigating hair growth disorder treatments.

Within recent years, the list of factors that have an impact on hair cycling and could be used as possible research targets has been constantly growing. The modulators of the hair cycle are grouped in table 1 [2].

As indicated above, PTH is one of the causative factors of a premature anagen-to-catagen/telogen transition [2]. Changes in the balance between anagen-promoting factors and factors inducing catagen (like PTH) result in hair growth dysregulation. All the regulatory factors are under investigation as potential hair growth promoters or inhibitors.

Hormonal Impact on Hair Growth Cycle

Hormones affect follicular mesenchymal-epithelial interactions: altering growing time, dermal papilla size, dermal papilla cell, keratinocyte and melanocyte activity [2]. A better understanding of these mechanisms should improve the treatment of poorly controlled hair disorders. Androgens are the most important regulators of human hair growth. Also, thyroid function abnormalities and poor nutrition are the factors leading to hair growth disruption [30–32]. Recently, scientific curiosity has led to the development of an intensely expanding amount of knowledge concerning other hormonal impacts on hair

metabolism. Recently, the list of hormones, neurotransmitters and receptors expressed in the hair follicle, has been growing [33].

The Role of PTH and PTHrP in Hair Cycling

There is significant evidence that PTH and PTHrP influence the proliferation and differentiation processes of the epidermis and hair follicle (table 2). PTH is a polypeptide hormone secreted by the parathyroid glands, normally, as a response to serum calcium and phosphate levels [34]. PTHrP is in fact a polypeptide sharing 70% homology in the N-terminal fragment with PTH. It was first discovered in humoral hypercalcaemia of malignancy, as a protein produced by different tumours [35].

It has been proven that PTHrP and its mRNA are present in normal fetal and adult tissues, especially in organs with highly proliferating cells, such as bones, kidneys, the placenta, hair follicles and the skin [15]. The secretion of PTHrP in the skin was first identified over 20 years ago in human keratinocyte cultures [36]. Receptors for PTHrP and for PTH in the hair follicle have been localized in the dermal sheath and the dermal papilla of developing hair. Activation of PPR (receptors for PTH/PTHrP) in the hair follicle regulates the anagen-to-catagen transition of the hair cycle [2, 37].

It is well proven that the PTH/PTHrP signalling influences proliferation and differentiation of mesenchyme-derived cell types. The current hypothesis suggests that PTHrP is released by epidermal cells and migrates to

Table 2. Hormones/neurotransmitters and their receptors expressed in the hair follicle [4]

Melatonin/melatonin receptor [113]
Substance P/neurokinin receptor 1 [114]
Angiotensin receptor [115]
Corticotropin-releasing hormone (CRH)/CRH receptor 2 (CRH-2R) [116]
Growth hormone (GH)/GH receptor [117]
Adrenocorticotrophic hormone (ACTH)/melanocortin 1 receptor (MC-1R) [118]
α -Melanocyte-stimulating hormone (α -MSH)/MCR-1, MCR-5 [118]
Insulin-like growth factor 1 (IGF-1) [119]
Somatostatin receptor 5 [120]
Endothelin/endothelin receptor [121]
Parathyroid hormone-related protein (PTHrP)/parathyroid hormone receptor (PPR) [122]
Adrenomedullin/calcitonin receptor-like receptor [123]
Erythropoietin/erythropoietin receptor [124]
Leptin/leptin receptor [125]
Epidermal growth factor receptor [126]
Hepatocyte growth factor receptor [127]
Fibroblast growth factor (FGF)/FGF receptor (FGFR) [128]
Vascular growth factor [129]
Transforming growth factor β (TGF- β)/TGF- β receptor [127]
Luteinizing hormone (LH)/LH receptor [130]
Chorionic gonadotropin (hCG)/hCG receptor [130]
Platelet-derived growth factor (PDGF)/PDGF receptor [127]
Androgens/androgen receptor [131]
Oestrogens/oestrogen receptor [131]
Progesterone/progesterone receptor [131]
Glucocorticoid/glucocorticoid receptor [132]
Aldosterone receptor [133]
1,25-Dihydroxyvitamin D receptor (VDR) [134]
Endocannabinoids/endocannabinoid receptor [135]
Prostaglandin E ₂ /EP [136]
Prostaglandin F _{2α} /FP [136]
Prostaglandin D receptor [137]
Prostaglandin I receptor [137]
Thromboxane A receptor [137]
Peroxisome proliferator-activated receptor γ (PPAR- γ) [138]
Retinoids/retinoid receptors [139]
Peroxisome proliferator-activated receptor α (PPAR- α), β , σ (for FFA) [138]
Liver X receptors [140]

cross-act with the dermal portion, as these cells are equipped with PPR.

As PTHrP shows paracrine activity in various tissues, the model of receptor signalling (PPR) is then discussed. Two different types of PTH/PTHrP receptors – the classic (type 1 PPR) and the unconventional one – are speculated. The classic receptors for PTHrP and PTH are found to be expressed on human dermal fibroblasts [38], while a specific one is present on keratinocytes [39]. The receptor for PTH/PTHrP is a G-protein-coupled receptor which transduces the signal through adenylyl cyclase or phospholipase C second messenger pathways [40]. Surprisingly, in some tissues PPR has no effect on protein

kinase A/protein kinase C pathways. However, in these cells, like in the dermal papilla, PPR signalling still alters proliferative functions through tyrosine phosphorylated protein [41].

The expression of PTH/PTHrP and its receptor (PPR) in the hair follicle is, as suspected, variable during the hair cycle, depending on the metabolic status. The PTHrP mRNA level decreases in early anagen and then peaks during late anagen, where transcripts of PTHrP are found in the outer root sheath of the non-permanent portion of the hair follicle [41]. It must be noted that the non-permanent portion of the hair follicle undergoes apoptosis during catagen [42]. On the other hand, PPR mRNA ex-

pression, which is highest during angiogenesis, is relatively low in adulthood, only increasing during early anagen in the connective tissue sheath that surrounds the growing hair follicle [41]. The PTH/PTHrP signalling pathway is then, as it has already been said, the next part of the complex epithelial-mesenchymal cross-acting regulation of hair cycling [42].

Numerous studies confirmed the suspected role of PTH/PTHrP as a proliferation-regulating factor. First, human PTHrP(1–34) peptide and human PTH(1–34) have been shown to inhibit proliferation and induce terminal differentiation of cultured human keratinocytes [43]. Next, applying the PTH antagonist, a bovine PTH (7–34) amide to these cells resulted in reduced proliferation and inhibited cornified envelope formation. Incorporation of thymidine, as a marker of the studied cells' proliferation, exhibited alterations, which further confirmed the potent antiproliferative role of PTHrP [34].

Through investigations into the mechanisms of antiproliferative activity of PTH/PTHrP, it has been found that the N-terminal portion of PTHrP (a fragment similar to PTH) has also been reported to inhibit angiogenesis in endothelial cells *in vitro* when there is an overexpression of PTHrP reduced tumour vascularization *in vivo* [42]. The next evidence for this specific way of action of PTHrP is that premature angiogenesis is also found as a problem leading to the chondrodystrophy associated with PTHrP and PPR knockout mice [44]. Transgenic mice overexpressing PTHrP (K14-PTHrP mice) with a measured 10-fold increase in PTHrP content in the skin, but with no hypercalcaemia/PTHrP in the circulation, presented disturbances in hair follicle growth and function. In these mice, the ventral skin almost completely lacked hair follicles, and the dorsal coat was shorter and thinner in adulthood [37]. This was apparently the result of a primary failure of follicle induction in the studied transgenic K14-PTHrP mice, and it confirmed an antiproliferative impact of PTH agonists. An interesting phenomenon was that the phenotype presented by male transgenic mice was less severe than that in females, which could, in the authors' opinion, suggest the protective role of androgens [45] but requires further studies [37]. Other immunohistological studies demonstrated the presence of PTHrP, most notably in developing tissues and also in developing skin appendages [46].

Summarizing, PTHrP overexpression leads to a shortened hair circle by reducing proliferation in the matrix during late anagen. As PTHrP has been proven to be a regulator of angiogenesis, the vasculature of the hair follicle in K14-PTHrP mice was, as suspected, also altered

[42]. It is understandable that anagen hair units need extensive angiogenesis for their highly proliferating cells [47]. In accordance with the suspected influence of decreased angiogenesis on the hair follicle diameter, a 33% decrease in vessel length and vessel diameter was observed during the study with transgenic mice that overexpressed PTHrP. On the other hand, in PTHrP knockout mice (lack of PTHrP/PPR expression) increased vasculature was observed [42]. There is still a question about the pathomechanism of the regulation of angiogenesis caused by PTHrP/PPR signalling. It was previously discovered that vascular endothelial growth factor expression is correlated with the regulation of the hair growth cycle [48]. However, in the study of Diamond et al. [42], no changes in the expression of vascular endothelial growth factor or fibroblast growth factor 2 accompanied a reduced vasculature in the KrP mice, so a direct influence of PPR signalling on angiogenesis is speculated.

The role of PTH/PTHrP signalling in skin and hair follicle physiology cannot be denied. Agonists and antagonists of PTH that connect to PPR alter the proliferation rate and the expression of differentiation markers *in vitro/in vivo* [34]. From this point of view, PTH antagonists have been suspected to be a possible target for scientists trying to discover a topical drug promoting hair growth *in vivo* [49].

Dermatological Manifestations of Parathyroid-Related Disorders

Despite the potent role of PTH as a regulating factor in the hair growth cycle, the dermatological manifestations of parathyroid-related disorders, and especially hair growth disorders, are rarely a subject of dermatologists' and endocrinologists' interest [5].

Sporadic cases of PTH-related hair symptoms were reported in familial syndromes of hyper-/hypoparathyroidism [50–52].

PTH, together with calcitriol, regulates calcium and phosphate homeostasis [53]. Therefore, the majority of symptoms of hypo- or hyperparathyroidism could be caused by hypo- or hypercalcaemia. Parathyroid glands respond to alterations of calcium concentration in serum through their calcium-sensing receptors. These receptors are expressed in the parathyroid glands and also in highly proliferating tissues [54]. Parathyroid disorders are generally divided into hypo- and hyperparathyroidism.

Sporadic primary hyperparathyroidism is still the most frequently occurring among parathyroid-related

diseases [55]. The inherited cases include isolated hyperparathyroidism (with hyperparathyroidism-jaw tumour syndrome), familial benign hypercalcaemic hypocalciuria and the group of multiple endocrine neoplasia (MEN) syndromes [53]. Hypoparathyroidism is associated with sporadic hypoparathyroidism, hypoparathyroidism associated with polyglandular failure, pseudohypoparathyroidism and autosomal dominant hypocalcaemia.

Hyperparathyroidism and Its Dermatological Manifestations

Hyperparathyroidism is diagnosed in the case of an inappropriate secretion of PTH with a coexisting increase in calcium serum concentration. In sporadic cases, primary hyperparathyroidism affects mostly women, in their mid-50s, who are usually asymptomatic. The first sign of this condition is usually an incidentally detected hypercalcaemia. Sporadic hyperparathyroidism is associated with a single adenoma in approximately 80% of cases or with multiple adenomas in 2–4% of cases. It could also be caused by hyperplasia of the parathyroid glands in 10–15% of cases, or be related to parathyroid carcinoma in 1–2% of cases [55]. Despite the molecular role of PTH, which can regulate the proliferative activity of skin appendages, such as hair follicles, there is still a lack of evidence that skin and hair abnormalities are directly related to primary hyperparathyroidism. An exception may be metastatic calcifications associated with hypercalcaemia [53]. And also, a relation with chronic urticaria has been described in a few case reports [56].

Hereditary disorders of hyperparathyroidism are familial isolated hyperparathyroidism, hyperparathyroidism-jaw tumour syndrome and multiple neoplasia syndromes. In familial isolated hyperparathyroidism and in hyperparathyroidism-jaw tumour syndrome, skin and hair abnormalities were not observed [57, 58]. MEN type 1 (MEN1) includes: hyperparathyroidism in almost 90% of cases, pancreatic tumours in 40% of the cases, and pituitary tumours in 20% of cases (especially as prolactinoma, foregut carcinoid or adrenal tumours). It is also commonly connected with skin neoplasms. In MEN1, patients with facial angiofibromas could be noticed in 85% of cases, collagenomas in 70% of cases and lipomas in 30% of cases [59]. Angiofibromas and collagenomas are almost always specific for MEN1 diagnosis. Starting in the second decade of life, angiofibromas in MEN1 are located on the lips and centrally on the face, presenting as multiple, a few millimetres in a diameter, skin-coloured, ery-

thematous papules. Collagenomas are located usually on the trunk and neck, presenting as skin-coloured papules and nodules, either as solitary or more numerous lesions. Other skin findings include single or multiple lipomas, cafe-au-lait lesions or hyperpigmentations. In case of other hormonal disturbances acanthosis nigricans, acrochordons and other hormone-related skin lesions could be present. Hair loss in patients with MEN1 is highly expected, especially in the case of prolactinoma; however, researchers' descriptions of this syndrome almost constantly miss the hair growth problem [53]. The MEN2a syndrome (Sipple's syndrome) includes medullary thyroid cancer (which is present in 100% of the cases), pheochromocytoma (seen in 40% of patients) and primary parathyroid hyperplasia (noticed in about 10–20% of cases). MEN2a is associated with mutations in the RET protooncogene. This syndrome is inherited in an autosomal dominant manner. The symptoms of MEN2a include medullary thyroid cancer, pheochromocytoma and (in 10–20% of patients) primary parathyroid hyperplasia. The latter seems to be associated with cutaneous macular and lichen amyloidosis. Skin lesions in these cases are located predominantly in the interscapular area as pruritic, scaly, lichenoid and hyperpigmented papules with histopathology of lichen amyloidosis [53, 60]. In MEN2b syndrome, medullary thyroid cancer is also the most dominant feature, being associated with pheochromocytoma, but without (or very rarely with) hyperparathyroidism. The genetic diagnosis of MEN2a and MEN2b is obligatory to identify the asymptomatic family members with the mutation in the RET proto-oncogene. If the mutation is present, a prophylactic strumectomy is provided as the medullary thyroid cancer is still life-threatening [61].

Secondary hyperparathyroidism (in the case of renal failure) is connected with multiple symptoms of the underlying end-stage renal disease. Hyperparathyroidism is the result of hyperphosphataemia and hypocalcaemia that stimulate the parathyroid glands' growth and secretion leading to hyperplasia or multiple adenomatosis of the parathyroid glands. Pruritus and metastatic calcifications are the most frequent dermatological symptoms in this case [62, 63]. Generally, in the condition of altered calcium and phosphate serum concentrations, calcinosis cutis could be present in all parathyroid disorders, with the highest prevalence in the case of renal failure. It is seen as benign, firm, white nodules/papules that could resolve after stabilization of calcium-phosphate homeostasis, or it could lead to calciphylaxis and necrosis of the skin [64]. Foci of skin calciphylaxis are usually noticed in the case of end-stage renal failure and in the case of secondary or

tertiary hyperparathyroidism; however, it is seldom presented in the case of primary hyperparathyroidism [65].

Hyperparathyroidism tends to be cured radically by parathyroidectomy, which should be recommended to all symptomatic patients. However, through observation, evaluation and stabilization of hormonal homeostasis, in conjunction with the evaluation of the clinical and genetic diagnosis, it can be decided what kind of management should be provided in each individual case [66]. Skin manifestations, such as angiofibromas, collagenomas and lipomas, noticed mainly in MEN syndromes, can be surgically excised for cosmetic indications. Angiofibromas may be treated with pulsed dye, KTP (potassium titanyl phosphate; KTiOPO_4) or CO_2 lasers [53]. The most complex patients are those with secondary hyperparathyroidism related to renal failure with multiple symptoms and severe dysregulation of systemic homeostasis. The most important here is still systemic treatment aimed at obtaining hormonal and mineral homeostasis [53].

As hair growth disorders often go unreported in a large group of patients with hyperparathyroidism, the question about the real presence or absence of hair growth disturbances in case of elevated PTH arises.

Hypoparathyroidism and Its Cutaneous Manifestations

Hypoparathyroidism is diagnosed in case of hypocalcaemia, usually, with an inappropriate response of the parathyroid glands or, in case of elevated PTH levels, a lack of responsiveness to its effects, known as pseudohypoparathyroidism [52]. The most frequent, nowadays, is still the hypoparathyroidism secondary to thyroidectomy (with parathyroidectomy or in the case of fibrotic changes after surgery and decreased vascularization of the parathyroid glands). However, there are also cases of isolated idiopathic, congenital sporadic or inherited hypoparathyroidism (di George syndrome, Albright's osteodystrophy) or cases of hypoparathyroidism related to autoimmune disorders like autoimmune polyglandular syndrome type 1. In all cases of hypoparathyroidism, the symptoms are correlated with low serum-ionized calcium levels including paresthesia, muscle cramps, tetany, laryngo- and bronchospasm, extrapyramidal signs, seizures and dental abnormalities. Classically reported skin symptoms refer to dry, rough, keratotic and puffy skin [52]. The nails are noted to be ridged, with onycholysis. Hair is reported as coarse and brittle. Also, persistent or recurrent candidal infections of the skin or/and especial-

ly mucous membranes are thought to be associated with different types of hypoparathyroidism; however, typically they are noticed in multiple auto-immune endocrinopathies [53]. The induction of general psoriasis, pustular psoriasis or impetigo herpetiformis that are noticed in cases of hypoparathyroidism becomes understandable as PTH has been proven to regulate the proliferation of skin and hair follicles [67, 68]. Unfortunately, although subcutaneous PTH injections have been proven to be safe and effective in the treatment of parathyroid-related symptoms, such therapy has not received Food and Drug Administration approval for the indication of hypoparathyroidism.

As in hyperparathyroidism, the suspected hair growth abnormalities are rarely reported. There are single studies that show a significant prevalence of hair loss in patients with hypoparathyroidism. In a study of 25 patients with a symptomatic permanent hypoparathyroidism (following surgery), skin and hair symptoms were estimated to be present in 68% of patients, causing a greater impact on the quality of life than other symptoms related to hypocalcaemia, such as paresthesia, joint pain and osteoporosis [69].

The results of another study also correspond to the direct role of PTH in the skin and its appendages. In a studied group of 21 patients with hypoparathyroidism secondary to surgery, mucocutaneous symptoms were noticed in more than 76% of patients, and symptoms related to hair growth abnormalities were the most frequent among them. In fact, axillary hair loss was found in 61.9% of patients, loss of pubic hair in 52.38% of patients, and coarsening of body hair was detected in 47.62% of patients. Additionally, alopecia areata was present in 9.52% of the studied patients. Other mucocutaneous findings included brittle, ridged nails leading to onycholysis, dry, xerotic skin, pustular psoriasis, acneiform eruption and bullous impetigo. Surprisingly, the symptom most commonly associated with hypoparathyroidism, oral candidiasis, was found only in 1 patient [70].

Trichoscopy in Patients with Parathyroid Gland Disorders

Trichoscopy is dermoscopy of the hair and scalp. Analysis of different structures, which is performed during a trichoscopy examination, includes the evaluation of hair shafts, hair follicle openings (dots), perifollicular epidermis and blood vessels. This method allows for a differential diagnosis of various causes of hair loss [71]. As

PTH may facilitate the anagen-to-catagen/telogen transition and induce telogen effluvium, trichoscopy in these patients will show features typical of telogen effluvium of other origin, such as a decrease in hair shafts per follicular unit, perifollicular discoloration and upright regrowing hairs [71]. It must be highlighted that the majority of patients with hyperparathyroidism are middle-aged and postmenopausal women, so differentiating it from androgenetic alopecia and senescent alopecia is crucial. Research studies are ongoing to identify whether there are more characteristic features of hair conditions in the course of hyperparathyroidism, which can be identified or diagnosed by trichoscopy.

PPR Ligands as a Potential Treatment Option for Hair Disorders

The hair follicles are an interesting target for topical drugs [72–74]. The putative role of PTH/PTHrP and PPR signalling suggests that PPR ligands could be candidates for topical drugs that can stimulate or inhibit hair growth. However, PTH and PTHrP are very unstable peptides, so it is difficult to create topically deliverable PTH/PTHrP drugs. As the antagonists of PPR show a stimulating effect on the proliferation of hair follicle cells, they are an interesting potential target for researchers [75–77]. Safer et al. [49] attempted to apply PTH(7–34) – antagonist of PPR – topically to the skin of SKH-1 hairless mice. SKH-1 mice lose all external hair in their first hair cycle after birth. Promisingly, after 1 week of treatment, a stimulation of hair growth was observed. When compared to the study control group, the hairs were 216% longer and a 40% increase in the number of hairs was reported. On average, 43% more hair follicles stained positive with H-thymidine incorporation and 5-bromo-2-deoxyuridine into DNA as markers of active proliferation. There was no difference in serum calcium concentration between the PTH(7–34)-treated mice and the controls, indicating that there were no systemic adverse effects of this topical therapy. The increase in hair growth after treatment with PTH antagonist, applied topically as a liposome cream, was very promising for further research [49]. It may be hypothesized that PTH antagonists are a potential treatment option in hair loss disorders.

Also, the proliferation-inhibiting effect of PTH/PTHrP agonists may be beneficial in clinical practice. PTH/PTHrP agonists were used as effective experimental treatment for psoriasis. A cream created with PTH(1–34) – an agonist of PPR – inhibited the patho-

logical hyperproliferation of the skin [75]. It may be hypothesized that PTH antagonists may be a potential treatment option in hair loss disorders [75].

PPR Agonists and Antagonists as a Potential Treatment Option for Chemotherapy-Induced Alopecia

PTH agonists and antagonists have been shown to improve hair growth after chemotherapy. Chemotherapy of cancer patients evokes many side effects, and chemotherapy-induced alopecia (CIA) is, in fact, one of the constant adverse side effects of a cancer therapy [78, 79]. CIA results in a depressed mood, causes stress and a high level of discomfort for treated patients [80, 81]. The incidence and severity of CIA vary depending on personal susceptibility and the chemotherapy protocol, but the general prevalence of CIA is estimated to be in the range of 65–85% in patients receiving chemotherapy [82]. Hair loss in this condition is associated with an impaired regrowth of hairs, which are thinner and more fragile. The mechanisms considered to be connected with this process are also multiple and depend on the type of chemotherapeutic agent. However, CIA is usually linked to apoptosis-related damage of the hair follicle [83]. Many cytostatics act also by decreasing proliferation of the hair follicle, where, as it is already known, the PTH-PPR signalling is a potent way to alter the proliferative activity [45]. Treatment of CIA is highly needed, but there are still no recommended models of treatment. The only one, and which is still controversial, could be scalp hypothermia during chemotherapy courses [84].

PTH agonists and antagonists which are proven to alter hair growth have been tried in this problematic hair loss disorder. It was shown that both PTH agonists and antagonists effectively altered the hair follicle response to CIA in a depilated mouse model. However, the regrowth of hair was dependent on a frequent intraperitoneal injection of peptides, suggesting a dose-dependent effect and a problematic bioprofile of the administered drug [45]. In another study, Katikaneni et al. [85–87] combined PTH with a collagen binding domain (PTH-CBD) to promote the distribution and retention of PTH(1–33) agonist in well-vascularized, high-collagen-containing tissues, such as the skin. The results of that study are promising. A single dose of the peptide PTH(1–33) caused a hair regrowth in mice within 30 days and an increase in the number of anagen phase VI hair follicles. Surprisingly, PTH-CBD antagonists have no significant effect on hair

growth [88]. In another study, PTH agonists and antagonists were CBD-linked and applied subcutaneously to mice treated with cyclophosphamide. Hair damage caused by chemotherapy was prevented and a re-establishment of hair growth was obtained. In that study, PTH-CBD peptide also caused a repigmentation in patients with alopecia provoked by cyclophosphamide.

As there is still no approved or effective treatment for patients with CIA, PTH agonists or antagonists seem to be peptides with a promising potential in preventing CIA in early treatment [85, 86]. The PTH(7–34)-CBD and PTH-CBD subcutaneous injection in mice initially resulted in whole-animal distribution and, later, was followed by the redistribution of applied peptides to collagen-rich tissues such as bone and skin. No symptoms of hyperparathyroidism or calcium serum level alterations were found in the study [88]. The majority of hairs in the histopathological samples of treated mice stayed long in anagen VI, confirming the very potent role of the peptides used. It is noteworthy to mention that PTH-CBD could also be applied in the prophylaxis of reduced bone mineral density associated with chemotherapy. Such results were obtained in the *in vivo* study, where mice were treated with PTH-CBD subcutaneously before chemotherapy was started [88]. As parallel studies confirm, the antiproliferative impact of PTH agonists and the proliferative role of PTH antagonists in the results of the studies of Katikaneni et al. [85–88] (where both agonist and antagonist caused hair growth improvement in CIA) could be surprising. However, it must be remembered that PTH(1–34) peptide could have both an agonistic and antagonistic impact, and aminoterminal truncation has been shown to convert PTH from its agonist to antagonist form [89].

Study results had been so promising that clinical trials with topically administered PTH(7–34) applied in CIA were started in IGI Laboratories. However, despite great hope, the results of phase II clinical trials appeared to be disappointing, and the trial was stopped by the parent company IGI Laboratories [49]. The lack of the expected effect could have been related to rapid utilization, clearance and problematic distribution of PTH antagonistic analogues used in the treatment. It has to be underlined that the biological activity of the antagonist portion is much weaker than that of the PTH agonist portion. Additionally, the antagonist portion [PTH(7–34) amide] is more fragile and unstable. From this point of view, treatment efficacy with a PTH antagonist could be difficult to predict and may be dose dependent. However, clinical trials are now being performed with a purer antagonist peptide which is referred to as PTH(7–33) [49]. Summarizing

the current knowledge, PTHrP and PTH generally accelerate the hair cycle (initiate the anagen phase and evoke the transition from anagen to catagen). The reason for the differences in the way that agonists and antagonists of PPR act in the hair growth cycle has recently been discovered. Application of PTHrP agonists is beneficial in the case of inhibition of Wnt signalling (hairless mouse study, potentially androgenetic alopecia), as the agonists prolong the anagen phase by inhibiting anagen-to-catagen transitions. On the other hand, in the case of CIA and in the engrafted C3H/HeJ mouse model for alopecia areata, agonists could have more potential. They accelerate hair regrowth by stimulating replacement of damaged hair follicles. PTHrP antagonists may only provide short-term improvement by prolonging the anagen phase of existing follicles, but they end up inhibiting the hair cycle and reducing hair growth [16].

Conclusion

Hair disorders and hair loss are not life-threatening; however, they adversely affect self-confidence, self-esteem and quality of life. Until recently, clinically obvious hair growth disorders associated with parathyroid-related disorders had not been reported in the literature. In contrast to this lack of data, PPR agonists and antagonists have been shown to impact the hair growth cycle in numerous studies *in vitro* and *in vivo*. PTH/PTHrP antagonists were shown to stimulate proliferation of hair follicle cells and hair growth. Topical application of PPR ligands induced positive changes in hair growth, especially in CIA. These data may indicate that PPR ligands may be safe and potentially effective topical drugs in the prevention or treatment of CIA. Despite the molecular evidence for the significant role of PTH/PTHrP and their receptors in hair biology, the possible clinical use of these potent cell regulators remains to be determined.

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