HAIR GROWTH STIMULATORS AND INHIBITORS

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Key words: Hair growth cycle; Androgenetic alopecia; Alopecia areata; Telogen effluvium; Hirsutism; Hair growth inhibitors; Hair growth promoters;

Summary

Hair growth disorders are wide spread around the world. They do affect many men and women, influencing on their psychological wellbeing. Trade segment associated with treatments of hair growth disorders has been increasing in the last 10 years. There are many experiments concerning new agents, a lot of other actives are approved for treatment of hair growth disorders. Current paper shows mechanism of the hair growth cycle as disturbances of which cause hair loss or unwanted hair growth. There are presented information concerning miniaturization of hair follicle - what is connected with androgenetic alopecia, telogen effluvium - another form of hair loss is described as well. Authors collect also data from many studies, experiments published in literature concerning alopecia areata, an autoimmune disorder of cells of the anagen hair bulb attacked by lymphocytes.

Apart from listed hair loss disturbances authors try to explain mechanism of unwanted hair growth - hirsutism.

There are many approved agents; many others wait for approvalment for treatment of hair growth disorders. In last few years many agents are taken into account as potential hair loss inhibitors, or hair growth promoters, among them plant active agents are very interesting. By using many plant extracts is possible to treat almost every hair growth disorders.

Riassunto

Le disfunzioni nella crescita dei capelli rappresentano un problema a carattere internazionale che colpisce sia gli uomini che le donne creando anche problemi psicosomatici. Per cui negli ultimi dieci anni si è assistito all’aumento nella commercializzazione sia di prodotti che di principi attivi capaci di migliorare le 3 diverse disfunzioni legate ai capelli.

Questo studio mette in evidenza tutti i meccanismi legati sia alla crescita che alla caduta dei capelli. Sono presenti dati sulla miniaturizzazione del follicolo pilifero - comuni all’alopecia androgenetica e all’effluvium in fase telogen - e su altre forme di caduta dei capelli.

Gli autori riportano anche tutti i dati presenti in letteratura riguardanti sia l’alopecia areata che l’ec-
**INTRODUCTION**

Hair growth disorders become widespread problem. They are not life threatening, however they do influence on social interactions, as well as on patients psychological well being. Therefore trade segment associated with treatments of hair growth disorders has been increasing in the last 10 years. All the time new active ingredients are applied and tried as potential agents for treatment disturbances in hair growth. Current paper concerns promoters and inhibitors of human hair growth. Before such active compounds are presented important is to describe human hair growth cycle. Another important problem is a molecular mechanism of hair loss. Knowing mechanisms in which hair follicle undergoes during cycle, is possible to influence on particular stage and thus treat disorder directly.

Authors in very short review give description of mentioned mechanisms regulating disorders of hair growth. One can find below information concerning miniaturization of hair follicle – what is connected with androgenetic alopecia, telogen effluvium – another form of hair loss is described as well. Authors collect also data from many studies, experiments published in literature concerning alopecia areata, an autoimmune disorder of cells of the anagen hair bulb attacked by lymphocytes.

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There are many approved agents; many others wait for approval for treatment of hair growth disorders. In last few years many agents are taken into account as potential hair loss inhibitors, or hair growth promoters, among them herbal active agents are very interesting. By using many plant extracts is possible to treat almost every hair growth disorders.

**HAIR CYCLE AND ITS MECHANISM**

The hair follicle, the most complex “organ” of the human body undergoes cyclic changes. It is transformed between periods of growth – anagen, period of regression – catagen, rest stage – telogen and shedding period – exogen.

Before description of hair cycle is given, important is to present anatomy of hair follicle.

**Anatomy of hair follicle**

Anagen hair follicle is composed of a multicylindrical stem with hair shaft in the center, originated as an oval hair bulb [1]. Hair follicle one can divide into epithelial and mesenchymal parts. Epithelial part can be divided into inferior region (situated in the bottom of the follicle, where the hair bulb is situated) and upper permanent region.

At the base of the bulb lies Dermal Papilla (DP) – onion like, cluster mesenchymal cells [2]. DP influences on thickness, length of hair follicle. It determines the changes during hair growth cycle [3], thus it is frequently called “command center” of the follicle.

Within the hair bulb the keratinocytes of the hair matrix are located. They may differentiate into trichocytes with melanin granules, cells of the inner root sheath (IRS). The outer root sheath (ORS), hair matrix, hair shaft derive from epithelial stem cells in the bulge area [4] (Fig. 1).

The bulge stem cells are responsible for the generation of the new hair. Mesenchymal stem cells within the tissue sheath are some kind of source for new DP cells. Hair follicle contains also mast cell precursors [5], neuronal stem cells – of which neurons and blood vessels may be developed.
Hair Growth Stimulators and Inhibitors

![Fig. 1 Light photomicrographs of the structure of sectioned anagen stage human scalp hair follicle. (a) A full-length longitudinal section of a follicle (b) Higher-magnification photograph of the bulb region of a hair follicle. APM, arrector pili muscle; B, bulge; CTS, connective tissue sheath; CTX, cortex of hair shaft; CU, cuticle of hair shaft; DP, dermal papilla; E, epidermis; HS, hair shaft; IRS, inner root sheath; M, matrix; ORS, outer root sheath; S, sebaceous gland (adopted form [2]).]

**Hair Cycle**

Problem of hair cycling has been extensively investigated. A lot of factors were discovered to be responsible for stimulating or inhibiting cycle of hair growth [2-4, 6, 7].

As was written above hair cycle is the rhythmic change of the hair follicle through periods: anagen, catagen, and telogen [8, 9].

New hair shaft synthesis takes place only during anagen.

Anagen can be divided into six stages (anagen I – anagen VI) (Fig. 2) [10, 11]. During anagen epithelial cells differentiate into 8 different cell lines: ORS, companion layer, Henle’s layer, Huxley’s layer, cuticle of the IRS, cuticle of the hair shaft, shaft cortex, and shaft medulla.

At anagen onset (anagen I) an unknown signal from the dermal papilla direct transient proliferation of stem cells. During anagen signals from DP regulate the proliferation of matrix cells. Inducing of anagen depends on few key factors, i.e.: soluble proteins of the WNT family, STAT3 transcription factor, noggin. Developments of anagen “sub-stages” are caused by Sonic hedgehog, HGF, FGF7. Some of mentioned factors may keep DP in anagen - WNT signals (WNT3a, WNT7a) [7].

When the new shaft develops in anagen IV/exogen old hair is released from the follicle [2].

Transition from anagen to catagen period depends on the FGF5 (Fibroblast growth factor 5). In catagen stage massive programmed cells death is involved. Duration of that period is associated with transforming growth factor β1, β2 (TGF-β1, TGF-β2), and p75 neurotrophin receptor (p75NTR), neurotrophins NT3, NT4, as well as with retinoids and prolactin [4, 12, 13].

During catagen DP condenses and moves upward, comes to rest beneath the bulge. The lower two third of the epithelial follicle are destroyed, excluding DP (remains associated with the regressing follicle [2] – see Fig. 2). At this time club structure is developed at the base of hair, making possible retaining hair in the follicle. Factors like retinoid X receptor-α (RXRα) in the epidermis and vitamin D receptor (VDR) may be components of the pathway responsible for activating catagen [14].

Next period after regression stage is telogen – rest phase. Hair follicle remains in relative quiescence until intrafollicular and extrafollicular signals cause reactivation [4]. Under the influence of the factor (17β-Estradiol) hair follicle may stay in the telogen stage.

Processes of reactivation occur during period called exogen, regulation of which is connected with factors like protease cathepsin L and Msx-2. Some of mentioned processes, are presented in Fig. 2.
Signals from DP regulate the proliferation of matrix cells

Signal from the dermal papilla direct transient proliferation of stem cells

Anagen I

Intrafollicular and extrafollicular signal cause reactivation

Fig. 2 At anagen onset (anagen I) an unknown signal from the dermal papilla direct transient proliferation of stem cells. During anagen signals from DP regulate the proliferation of matrix cells. Old hair is released from the follicle as the new shaft develops (anagen IV/exogen). In catagen stage massive programmed cells death is involved. During catagen DP condenses and moves upward, comes to rest beneath the bulge. The lower two third of the epithelial follicle are destroyed, excluding DP (remains associated with the regressing follicle). Next period after regression stage is telogen – rest phase. Hair follicle remains in relative quiescence until intrafollicular and extrafollicular signal cause reactivation; B, bulge; C, club signal; CH, club hair; CTS, connective tissue sheath; DP, dermal papilla; E, epidermis; HS, hair shaft; IRS, inner root sheath; KZ, keratogenous zone; ORS, outer root sheath; S, sebaceous gland; M, matrix; (adopted from [2]).

DISTURBANCES IN HAIR CYCLE AND HAIR GROWTH DISORDERS

Hair growth disorders are the result of disturbances in hair cycle. There can be pointed three types of well-known hair losses. Androgenetic alopecia in men and women is the result of shortening of anagen stage in hair follicle cycle, increased hair loss (telogen effluvium) is accompanied by transformation of terminal to vellus hair follicles. While anagen stage is prolonged, and one can see conversion of vellus hair into terminal follicles, hirsutism is observed [4, 15].

Alopecia areata – another hair growth disorders is associated with autoimmune attack on the hair follicle cells.

Androgenetic alopecia

The most popular and most frequently occurring hair loss is androgenetic alopecia (AGA). AGA is connected with shortening of anagen period, prolongation of telogen, with miniaturization of hair follicle. Large terminal hair are transformed into thin, vellus hair. Normally, duration of anagen is 3 years, while telogen lasts 3 months; the
ratio of anagen to telogen hair is about 12:1. In androgenetic alopecia anagen period becomes shorter, with unchanged, or longer duration of telogen, and thereby the ratio of anagen to telogen is reduced [16, 17]. Described changes are connected with androgens, and are caused by a deregulation of the conversion of testosterone (T) to dihydrotestosterone (DHT) [18]. Reduction of T to DHT is mediated by enzyme 5α-reductase (5αR) via reduced cofactors like NADPH. There are two types of 5α-reductase, type I and II. Type II has been found in hair follicle on the scalp, and it has crucial role in hair growth regulation [19, 20].

Another important enzyme is the cytochrome P-450 aromatase enzyme. Aromatase is located in outer sheath of hair follicle. This enzyme converts androgens like testosterone to the estrogen: estradiol (Fig. 3). Nowadays the role of estrogens formed from aromatase is uncertain. They can suppress the severity of hair loss, or firstly aromatase may reduce the androgens formed in the hair follicle.

DHT has high affinity to bind to androgen receptor (in comparison to other androgens). Therefore genes that transform terminal follicles to miniaturized follicles are activating by hormone (DHT)-receptor complex [21].

Androgens influence on dermal papilla of hair follicle. In that main mesenchymal component paracrine signals stimulating and inhibiting hair growth are produced by affection of androgens, e.g.: Insulin-like growth factor-1 (IGF-1), positive mediator in epithelial cells, transforming growth factor-β-1 (TGF-β-1) – androgen induced epithelial cells growth inhibitor [22].

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**Fig. 3** Testosterone metabolic pathway in skin; Testosterone may be converted into 5α-dihydrotestosterone (DHT) by 5α-reductase, via reduced pyridine cofactor, nicotinamide adenine dinucleotide phosphate (NADPH), or may be transformed to Estradiol via cytochrome P-450 Aromatase; (adopted from [20]).
Vascular endothelial growth factor (VEGF) is produced as well [23]. It can be seen that by influencing on DP, androgens change the hair cycle – duration of particular stages of cycle and the size of the hair matrix [16], causing follicular miniaturization.

Many studies suggested that pathophysiology in women and men, is different. In women it may be associated with androgen excess, e.g.: in women with hirsutism, acne [24]. Important is that in women process of androgenetic alopecia is milder than in men. Female AGA is characterized by diffuse thinning of the crown and intact frontal hairline, thus in men is connected with recession of hair and vertex balding [25]. Differences in male and female androgenetic alopecia are caused by different level of 5α-reductase – lower in women, and cytochrome P-450 aromatase – higher in women.

Summarizing, androgenetic alopecia may be treated by influencing on the formation of DHT, i.e. inhibitors of 5α-reductase may be used as active agents. There is also possibility to stimulate cellular proliferation, to promote hair growth [26]. Potential agents one can find below.

The most popular and most widely used pharmaceutical used for AGA treatment is finasteride1 in dosage of 1mg for the treatment of androgenetic alopecia in men. Adverse effect may include decreased libido, erectile dysfunction. In women finasteride is contraindicated when they are or may become pregnant, because it may cause abnormalities in male fetus [31].

Minoxidil1 is a well-known promoter of hair growth. It acts on increasing the duration of anagen stage of hair growth cycle, and thus enlarges miniaturized hair follicles. From chemical point of view minoxidil is a piperidinopyrimidine derivative, it was primary presribed as a vasodilatory antihypertensive drug [32]. The mechanism of action is probably associated with the opening the potassium channels and increasing the proliferation and differentiation of epithelial cells in hair shaft [20, 27]. Studies carried out in cultured DP cells demonstrated that minoxidil stimulate the growth of hairs through proliferation and anti-apoptotic effects in the DP cells, what results in prolonging anagen period [33].

Now minoxidil is over the counter (OTC) in the USA. It is dosed in 2% concentration orally. Adverse effects are: tachycardia, angina pectoris, and fluid retention. In women in childbearing taking of minoxidil may be associated with hypertrichosis of the fetus and congenital anomalies. When applied topically adverse effects are mainly dermatologic, i.e. local irritation, itching, dryness, erythema [31].

There are also “unapproved” agents commonly applied for the treatment of AGA. One of them is spironolactone11. This compound is a steroid with the structure of a basic nucleus of 4 rings, with resemblance to the mineralcorticoids. It is an aldosterone antagonist that acts as a weak antiandrogen, it may influence on both androgen reductase and on androgen biosynthesis, inhibiting that last. Spironolactone does not

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1 Finasteride IUPAC name: N-(1,1-dimethylethyl)-3-oxo-4-[5-(1,2,4-triazolidin-2-yl)-1H-pyrazole-1-carboxamide
2 Minoxidil IUPAC name: 3-hydroxy-2-imino-6-[1-piperidyl]pyrimidin-4-amine
3 Spironolactone – INN name
offer the hair re-growth. Side effects of spironolactone are: hyperkalemia, gynecosmatia and gastrointestinal symptoms. Spironolactone is effective in preventing hair loss in AGA in women. Contraindications are: renal insufficiency, anuria, chronic renal impairment, hyperkalemia, pregnancy, abnormal uterine bleeding [26]. Women in childbearing must be warned of the potential of feminization of male fetus. It is dosed orally: 50 to 200 mg/day, with 100 mg/day preferred dose.

Flutamide is a nonsteroidal antiandrogen. After converting to 2-hydroxyflutamide is a competitive inhibitor of DHT for the androgen receptor binding [34]. Nowadays flutamide is used for prostatic cancer in men. Side effect when taken orally is hepatotoxicity, including progressive liver failure. Studies concerning usage flutamide as topical agent for treatment of alopecia are needed.

Progesterone, because of it similarity to testosterone, utilizes the same enzyme, 5α-reductase, and binds to the androgen receptor as well. It is mostly indicated for ovarian disorders and contraception.

It is given intramuscularly or orally. At 2% concentration applied topically is useful in the treatment of androgenetic alopecia [26]. Another well-known antiandrogen is cyproterone acetate. It is competitive agent to DHT for the androgen receptor binding. It is indicated for prostatic cancer, benign prostatic hyperthropy, and for inhibiting libido in sexually deviant behavior. After orally administration into pregnant animals, it blocks the action of androgens in male fetus, and induces a form of pseudohemaphroditism. Cyproterone acetate may be use for treatment of AGA in women, after taken orally it appears to stabilize the hair loss process [35]. Side effects include menstrual irregularities, weight gain, breast tenderness, loss of libido, depression, nausea, because of cited above experiments in animals, women during childbearing must be warned of the potential of feminization of male fetus.

Aminexil was developed by L’Oreal. After treatment with that OTC agent, percentage of telogen hairs decreased and anagen hairs increased. As was written above in AGA miniaturization of the hair follicle occurs. It may be caused by inflammatory fibroplasias of the dermal sheath. Aminexil is acting as an antifibrotic agent, resulting in decreasing in collagen formation around the hair follicle, and therefore increasing the survival of the follicle [36].

Apart form presented agents there are many that may influence either on mechanism inducing hair loss, precisely on androgens action, or on hair growth. To such products may be included prezatide copper, copper chloride some amino acids (arginine/L-arginine, cysteine/L-cysteine), biotin and folic acid [26].

Many herbal extracts have extensively been investigated as potential agents for AGA treatment. Park et al. [37] searched 5α-reductase inhibitors in oriental medicinal plants. They found that the extract of Thujae occidentalis semen (TOS) inhibited 5α-reductase in vitro. They applied also TOS extract to mice with androgenetic alopecia (AGA). These experiments showed that in group treated with 1% TOS extract alopecia pattern was not occurred. Study carried out by Park et al. showed that TOS extract might be used for treatment of male androgenetic alopecia [37]. Rho et al. [38] discovered that Asiasari radix extract had hair growth-promoting effect. Based on research carried on C57BL/6 and C3H mice, they concluded that extract of A. radix stimulated telogen/anagen transition when given.

- Flutamide IUPAC name: 2-methyl-N-[4-nitro-3-(trifluoromethyl)sphenyl]-propanamide
- Cyproterone acetate IUPAC name: 3β-Cyclopropyl-12-pregna-1,4,6-triene-3,20-dione 6-chloro-17-beta,2-benzo-dihydo-17-hydroxy.
- Aminexil IUPAC name: 2,4-diamino-pyrimidine-3-oxide
- Thujae occidentalis English name: Yellow cedar
- Asiasari radix English name: Asiasarum root
topically, and stimulated cellular proliferation. After investigation with cultured human DP cells they found that A. radix extract up-regulates VEGF expression and therefore promote hair growth [38].

Among botanical agent Sophora flavescens extract is also applied for alopecia treatment [39, 40]. Topical application of that extract on mice showed the earlier conversion from telogen to anagen [40]. Roh et al. [40] investigated also effect of sophora flavescens extract on the expression of several growth factors, those important in hair growth. After experiments in human hair DP cells they concluded that extract induced mRNA levels of IGF-1 and KGF in these cells. Furthermore Sophora flavescens extract showed inhibitory effect on the 5α-reductase type II (experiments with rat prostate as an androgen source) [40]. Presented data demonstrates that Sophora flavescens is another good candidate for an agent for treatment of hair growth disorders.

The most widely investigated botanical compound in treatment of androgenetic alopecia is Serenoa repens liposterolic extract (LSESr), and its components: β-sitosterols [41]. Interestingly dysfunction associated with AGA is similar to that concerning benign prostatic hyperplasia (BPH). Conversion of T to DHT by 5α-reductase, in the prostate gland, plays role in the development of BPH [42]. Because both AGA and BPH share similar hormonal pathways, it is possible to apply agents useful for BPH treatment as AGA inhibitors. To such agents Serenoa repens may be included [43]. LSESr is believed to be inhibitor of 5α-reductase, what was shown in several in vitro experiments carried out in cultured human foreskin fibroblast [44, 45]. As well treatments with β-sitosterols obtained from Serenoa repens were carried out. It is suggested that β-sitosterols may reduce T in the micro-milieu of 5α-reductase active tissues [44]. Prager et al. demonstrated studies on botanically derived inhibitors of 5α-reductase. Authors observed evidence of efficacy using orally administered Serenoa repens therapy in the treatment of AGA [44].

Apart from presented agents, interesting results in influencing on hair growth cycle may be obtained with molecular factors that naturally occur in hair follicle. Neurotrophins are example of such mediators. Neurotrophins 3, 4, and brain-derived neurotrophic factor (BDNF), molecular mediators of intra and perifolliucar signaling are able to stimulate premature catagen induction. BDNF (and its receptor tyrosine kinase B) act via TGFβ2 (transforming growth factor β2) upregulation [12]. Thus it is probably possible to modulate hair growth by tyrosine kinase B mediated signaling, what may be future therapeutic strategy for hair loss [4].

**Alopecia Areata**

Alopecia areata (AA) is an autoimmune disease. Alopecia areata affects both women and men, and is age unreliable, with much wider occurring in children and in young adults. Risk of alopecia is connected with family history [46, 47]. It may be associated with reversible small, roll patches hair loss, hair loss involving all the scalp hair – alopecia totalis, or scalp and body hair – alopecia universalis.

In that kind of hair loss cells of the anagen bulb are attacked by CD4 and CD8 lymphocytes. According to published data alopecia areata is T-cell mediated disease [46, 47]. Gilhar et al. [48] injected T-cells from patients into human skin grafted to immunodeficient mice, as a result peri-

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*Sophora flavescens* English name: Yellow mountain laurel

*Serenoa repens* English name: Saw palmetto
bulbar inflammation and hair loss occurred. Lymphocytes probably attack matrix keratinocytes, DP cells, and melanocytes [2]. Therefore anagen follicles enter dystrophic catagen and the hair shaft breaks off.

Treatment of alopecia areata is based on immunosuppressive agents [31], e.g. corticosteroids. They are known to inhibit activation of T-lymphocytes. Corticosteroids may be dose topical (e.g. in emulsion), intralesional, or systemic [49].

Glucocorticoids, dosed by intralesional injection, are the most popular treatment for alopecia areata. Example of such therapy is injection of triamcinolone acetonide. Sometimes effect may not be seen, because the glucocorticoid receptors in the scalp bind the inhaled glucocorticoids poorly [50].

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_Glycyrrhiza glabra_ extract contains chemically similar compounds to corticosteroids and as Batiuk presents in his article liquorice is a possible novel agent for AA [51].

Another example of therapy is immunomodulatory treatments. Anthralin, non specific, anti-Langerhans' cell effecting agent is an example of such therapy. Anthralin is irritating, and causes redness, itching, scaling.

Nowadays to that group diphenylcyclopropane and squaric acid dibutylester can be included, as well [49, 52].

Minoxidil - agent applied in androgenetic alopecia treatment is as well used for alopecia areata [31].

**Telogen effluvium**

_Telogen effluvium_ (TE) is another type of hair loss. In general is caused by synchronous entry of many follicles into exogen period [53]. In the literature one can find five functional types of TE described, i.e.: immediate anagen release, delayed anagen release, short anagen syndrome, immediate telogen release, and delayed telogen release [54]. In immediate anagen release hair follicles leave anagen and enter telogen prematurely with increase hair shedding, it may occur after physiologic stress, or be caused by drug. Delayed anagen release may be observed during pregnancy, when hairs remain in anagen and do not enter telogen, then it is possible (in the case when large number of follicles are involved) that increased shedding some months later may occur.

An idiopathic shortening of anagen duration causes short anagen syndrome - a persistent telogen hair shedding [53, 54].

Immediate telogen released is a result of shorter than normal telogen duration.

Finally while prolonged telogen follows by transition to anagen delayed telogen released occurs. In human is rare, and it occurs seasonally [53, 54].

In some articles to mentioned five types of TE chronic telogen effluvium is added.

TE has been reported in patients with iron deficiency and thyroid disorders. It is reported that many other drugs, e.g. beta-blockers, antihyperlipemic drugs, nonsteroidal anti-inflammatory drugs, anticoagulants may cause telogen effluvium as well. There are no controlled studies with iron supplementation, or with thyroid hormone supplementation [32].

**Hirsutism**

_Hirsutism_ - the excessive growth of terminal hair on the face and body of a female in a typical male pattern distribution become wide spread problem [55, 56]. As Rittmaster presented almost half of American women complain of

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1. Triamcinolone acetonide IUPAC name: 9-fluoro-11,16,17-trihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydrocyclopenta[a]phenanthrene-3-one
2. Glycyrrhiza glabra English name: Liquorice
3. Anthralin IUPAC name: 1,8-dihydroxy-10H-anthracen-9-one (INCI: Glycyrrhiza glabra)
4. Squaric acid dibutylester IUPAC name: 3,4-Dihydroxy-3-cyclopentene-1,2-dione
unwanted facial hair [57]. Hirsutism is caused by increased sensitivity of the skin to androgens, as a result of increased activity of peripheral 5α-reductase, enzyme that convert testosterone to dihydrotestosterone.

Apart from such methods like mechanical hair removal, i.e. shaving, plucking, waxing, and depilatory creams, therapy with peripheral androgen blockers is an effective way for hirsutism treatment. Several agents are applied for such treatment: cyproterone acetate, spironolactone, flutamide, androgen receptor antagonists [55, 56, 58]. Finasteride - 5α-reductase inhibitor is recommended to combine with an oral contraceptive to avoid feminization of a male fetus [59].

Novel agent to fight hirsutism is eflorentinite. Action of that topically applied agent refers in an irreversible catalytic inhibiting of ornithine decarboxylase, enzyme responsible for catalyzing of first step in the biosynthesis of polyamines. Such polyamines like puterscine, spermidine and spermine are required for cell division and differentiation [60] in the tissues like the hair follicles. Eflorentinite influences on hair growth, because it affects the length, diameter and composition of the hair's fiber [56, 60]. Eflorentinite should not be used in the patients before 12 years of age, women in childbearing. It may alter the fetus development, and, what is not known whether or not it is excreted in human milk [60]. Adverse effects are associated with oral administration, i.e.: anemia, diarrhea, leukopenia. There are no evidences of adverse effects when eflorentinite is dosed topically [60].

Interesting agents reducing hair growth and hair follicle dimensions are soybean-derived serine protease inhibitors. Two serine protease inhibitors (soybean trypsin inhibitor, STI, and the Bowman-Birk protease inhibitors) induce skin depigmentation, furthermore it is possible that reduce rate of hair growth and dimension as well. Topical trypsin treatment, after depilation induced cell death at the follicular papilla, what is resulted in delaying hair growth and pigmentation [61].

**SUMMARY: MANIPULATION OF HAIR CYCLE AS A KEY OF TREATMENT OF HAIR GROWTH DISORDERS**

As it is presented common hair growth disorders raised form disturbances in hair cycle. Manipulation in hair cycle may be used for treatments of hair growth disorders. Inhibition of anagen/catagen transition, and stimulation of telogen anagen transition, could be used for treatment of *androgenetic alopecia* and *telogen effluvium*. That type of hair loss, caused by drugs or metabolic disturbances may be treated as well by inhibition of telogen/exogen transition. Vice versa stimulating of anagen/catagen and inhibiting telogen/anagen transitions should be taken into account in *hirsutism* treatment. *Alopecia areata* disorder connected with autoimmune attack on hair follicles could be treated by inhibiting anagen/catagen transition; to prevent progression of that disease inhibiting of telogen/anagen transition is useful (Fig. 4).

Using similar scheme the treatments of different types of hair growth disorders may be presented (Fig. 5). There are shown well-known drugs like minoxidil, finasteride, as well as potential new agents for treatments of hair growth disorders, e.g. botanical extracts.

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Eflornithine IUPAC name: 2-difluoromethyl 2,5-diamino pentanoic acid
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**Fig. 4** Manipulation of hair cycle may be used for management of hair growth disorders. For treatment of androgenetic alopecia (AGA), telogen effluvium (TE), alopecia areata (AA) and hirsutism (H): inhibition (-) or stimulation (+) of transitions between hair cycle periods may be useful (based on [4]).

**Fig. 5** Agents triggering on hair growth cycle, used for treatment of hair growth disorders. Scheme presents only few drugs and potential agents for treatment in future: inhibition (-) or stimulation (+) (see references [4, 62]).
In the summary one can find collected agents, potential agents for hair growth disorders treatment, as well (Table I).

Hair loss, unwanted hair growth become wide spread problem around the world. Although hair growth disorders are not life threatening, however they do influence on patients psychological wellbeing. That implicates huge growth in trade segment concerning hair growth disorders. As it is presented in current paper there are many agents that trigger on hair growth cycle and therefore treat hair loss, or unwanted hair growth. Apart from well-known drugs there are also novel potent agents that may modulate hair growth, what may be future therapeutic strategy for hair loss, unwanted hair growth.

### Table I

<table>
<thead>
<tr>
<th>Agent</th>
<th>Hair disorder</th>
<th>Mechanism of action</th>
<th>Application form</th>
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<tbody>
<tr>
<td>Extract of <em>Tulasia occidentalis</em></td>
<td>Androgenetic Alopecia</td>
<td>Inhibition of 5α-reductase <em>in vitro</em></td>
<td>Topically</td>
</tr>
<tr>
<td><em>Aristoxorus radiis</em> extract*</td>
<td>Androgenetic Alopecia</td>
<td>Increase cellular and protein synthesis, induce telogen – anagen transitions</td>
<td>Topically</td>
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<td><em>Sophora flavescens</em> extract*</td>
<td>Androgenetic Alopecia</td>
<td>Inhibition of the 5α-reductase type 2, induced mRNA levels of IGF-1 and KGF in these cells increasing therefore hair growth</td>
<td>Topically</td>
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<td><em>Serena repens</em> liposterolic extract</td>
<td>Androgenetic alopecia</td>
<td>Inhibition of 5α-reductase, inducing telogen – anagen transitions</td>
<td>Topically</td>
</tr>
<tr>
<td>Finasteride</td>
<td>Androgenetic Alopecia</td>
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<tr>
<td>Minoxidil</td>
<td>Androgenetic alopecia</td>
<td>Increasing the duration of anagen; Increasing the proliferation and differentiation of epithelial cells in hair shaft</td>
<td>Topically, Orally</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Androgenetic alopecia</td>
<td>Influence on both α-reductase and on androgen biosynthesis</td>
<td>Orally</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Androgenetic alopecia</td>
<td>Bind to the androgen receptor</td>
<td>Topically</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>Androgenetic alopecia</td>
<td>Competitive agent to DHT for the androgen receptor binding</td>
<td>Orally</td>
</tr>
<tr>
<td>Aminexil</td>
<td>Androgenetic alopecia</td>
<td>Anti-fibrotic agent</td>
<td>Topically</td>
</tr>
<tr>
<td>Glucocorticoids, corticosteroids: e.g.</td>
<td>Alopecia Areata</td>
<td>Inhibition of the activation of T-lymphocytes</td>
<td>Intraleisional injection</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>Alopecia Areata</td>
<td>Probably: Inhibition of the activation of T-lymphocytes</td>
<td>-</td>
</tr>
<tr>
<td><em>Glycyrrhiza glabra</em> extract*</td>
<td>Alopecia Areata</td>
<td>Contact sensitization</td>
<td>Topically</td>
</tr>
<tr>
<td>Diphenylcyclopropene</td>
<td>Alopecia Areata</td>
<td>androgen receptor antagonists</td>
<td>Orally</td>
</tr>
<tr>
<td>Cyproterone acetate, Spironolactone, Flutamide,</td>
<td>Hirsutism</td>
<td>5α-reductase inhibitor</td>
<td>Recommended to combine with an oral contraceptive to avoid feminization of a male fetus</td>
</tr>
<tr>
<td>Finasteride</td>
<td>Hirsutism</td>
<td>5α-reductase inhibitor</td>
<td>Orally, topically</td>
</tr>
<tr>
<td>Effiplathine</td>
<td>Hirsutism</td>
<td>Irreversible catalytic inhibiting of ornithine decarboxylase, enzyme responsible for catalyzing of first step in the biosynthesis of polyamines required for cell division, and differentiation in the hair follicle</td>
<td>Orally, topically</td>
</tr>
<tr>
<td>Soybean derived serine protease inhibitors</td>
<td>Hirsutism</td>
<td>Induces cell death at the follicular papilla</td>
<td>Topically</td>
</tr>
</tbody>
</table>

*During experiments*
References


41) Saw Palmetto (Serenoa repens) and One of its constituent sterol beta-sitosterol. NTP materials, available at: http://ntp.niehs.gov, August 2006


Hair Growth Stimulators and Inhibitors


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