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PRACA POGLĄDOWA
REVIEW

The role of 5-α-reductase inhibition in supressing progression of male androgenetic alopecia − a postulate for further studies on possible application of saw palmetto extracts

Rola inhibicji 5-α-reduktazy w zatrzymaniu postępu łysienia androgenowego u mężczyzn – postulat na rzecz badań nad zastosowaniem ekstraktów z palmy sabałowej

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ABSTRACT

The study presents the mechanism of male androgenetic alopecia (MAGA), with a focus on the role of the enzyme 5-α-reductase, which is responsible for converting testosterone, the primary male hormone, into its active form, dihydrotestosterone (DHT). The consequences of the DHT stimulation of androgen receptors (ARs) located in the X chromosome of dermal papilla cells (DPCs) are described. This leads to androgen-induced gene transcription, disrupted hair follicle nourishment, and most importantly, an accelerated transition from the anagen to the catagen phase. The study also discusses how this enzyme can be targeted by molecules acting as inhibitors.

Furthermore, the justification for conducting more in-depth studies on the mechanisms of action involving extracts of saw palmetto (*Serenoa repens*) and their inhibitory effects on 5-α-reductase is presented. The study also advocates the identification and measurement of active substances present in saw palmetto extracts, with two promising phytosterolic compounds, stigmasterol and β-sitosterol, due to their demonstrated inhibitory activity on 5-α-reductase in extracts from other plant species.

As part of the proposal to deepen the research, attention is drawn to the need to investigate the impact of saw palmetto extract on the hair growth cycle, hair follicle life cycle, various growth factors and angiogenesis, immune system activity, and oxidative stress. Other areas of observation for the action of saw palmetto extracts could include their use in combination with other plant extracts or therapeutic agents such as platelet-rich plasma or fibrin-rich plasma.

KEYWORDS

5-α-reductase, androgenetic alopecia, dihydrotestosterone, hair follicle, inhibitors, saw palmetto, steroids, sterols

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STRESZCZENIE

W pracy przedstawiono mechanizm łysienia androgenowego u mężczyzn (*male androgenetic alopecia* – MAGA) z uwzględnieniem roli enzymu 5-α-reduktazy, która odpowiada za konwersję testosteronu, najważniejszego hormonu męskiego, do jego aktywnej formy – dihydrotestosteronu (DHT). Opisane zostały konsekwencje pobudzenia przez DHT receptorów androgenowych (*androgen receptors* – ARs), zlokalizowanych w chromosomie X komórek linii brodawkowej (*dermal papilla cells* – DPCs). Powoduje to transkrypcję genów uruchamianą przez androgeny, zostaje zaburzone odżywianie mieszka włosowego, ale przede wszystkim przyspieszeniu ulega moment zakończenia anagenu i przejścia do fazy katagenu. Przedstawiono również, w jaki sposób enzym ten może być poddawany działaniu molekuł pełniących funkcję jego inhibitorów.

Ponadto zaprezentowano uzasadnienie dla prowadzenia bardziej dogłębnych badań poświęconych mechanizmom działania, w których ekstrakty palmy sabałowej (*Serenoa repens*) wywołują efekt inhibicji 5-α-reduktazy. Dodatkowo w pracy został zawarty postulat na rzecz rozpoznawania i pomiaru substancji aktywnych znajdujących się w ekstraktach palmy sabałowej, w tym dwóch najbardziej obiecujących związków fitosterolowych – stigmasterolu i β-sitosterolu – ze względu na udowodnioną już aktywność inhibitorową w stosunku do 5-α-reduktazy w ekstraktach z surowców pochodzących z innych gatunków roślin.

W ramach postulatu na rzecz pogłębienia badań zwrócono uwagę na konieczność oceny wpływu stosowania ekstraktów z palmy sabałowej na cykl życia włosów, cykl życia mieszka włosowego, różne czynniki wzrostu i angiogenezę, a także aktywność układu immunologicznego czy stres oksydacyjny. Inne obszary obserwacji działania ekstraktów z palmy sabałowej mogłyby obejmować ich zastosowanie w terapiach w połączeniu z innymi ekstraktami roślinnymi lub środkami terapii, np. z osoczem bogatopłytkowym czy osoczem bogatym w fibrynę.

SŁOWA KLUCZOWE

5-α-reduktaza, łysienie androgenowe, dihydrotestosteron, mieszek włosowy, inhibitory, palma sabałowa, sterydy, sterole

Introduction

In this study, the authors will draw attention to the topic of male androgenetic alopecia (MAGA) as a condition of hair located on the head scalp, which is triggered by the conversion of testosterone into dihydrotestosterone (DHT) by 5-α-reductase. DHT molecules, after binding to androgen receptors (ARs), create ligand-receptor complexes that enter the nuclei and trigger androgen--dependent gene transcription, shortening the anagen phase, leading to systematic thinning of the hair.

This study, apart from an analysis of the enzyme--hormonal pathways in the initial appearance of MAGA and its progression, there is a call for further analysis of how saw palmetto extracts could be applied to tackle this condition. Saw palmetto (*Serenoa repens*) extracts are a promising inhibitor of 5-α-reductase – an enzyme that converts testosterone into harmful DHT [1]. The relieving effects of saw palmetto extracts have been seen in many studies in relation to benign prostate hyperplasia, or benign forms of prostate cancer and lower urinary tract symptoms [2,3]. Unsurprisingly, the same effects are observed in studies observing male participants with androgenetic alopecia (AGA) owing to the expression of 5-α-reductase in various body regions, such as the sexual organs and head scalp in this case [4]. Many studies confirm the therapeutical macro- and microscopic positive outcomes of saw palmetto extract application in MAGA, which show an increased number of new hair follicles and new hair in the anagen phase, leading to the recovery of hair density in the affected scalp areas [5].

Alas, there is a low level of interest in the acknowledgement and recognition of how actions are going in many clinically significant directions: which 5-α-reductase inhibitors in saw palmetto extracts are the key to successful therapies, and how the extract after application interplays with the molecular pathways of the hair follicle and hair life cycles, be it oriented towards regulation of the life cycle, growth or angiogenesis factors, hormones, immunological factors or oxidative stress.

Academic and therapeutical interest in AGA has been growing for years. There is no evidence that the occurrence of AGA among the population has increased; however, there are indirect indicators that may support speaking so: dietary habits, obesity, the quality of food, water and air, electromagnetic fields (including UV radiation), civilizational chronic illnesses, the outbreak of hormonal health deficiencies, and exposure to stress [6,7]. All of these factors may be overwhelmingly strong and comprise a multifactorial background for the etiology of AGA [8].

Ho et al. [9] claim that the occurrence of AGA may be up to 50% of male and female populations in various countries and vocational backgrounds. Tyszkiewicz et al. [10] argue that the occurrence of AGA grows up to 80% in males and 50% in females in their seventies. The internal sex-determined structure of AGA is distributed as the ratio 2 : 1 between males and females, respectively; nevertheless, there are many studies that present quite data different depending on – but not limited to – age, country, or comorbidities [7,11].

Male pattern baldness is linked to a well-defined chain of events between testosterone, the enzyme 5-α-reductase, DHT and ARs. The role of 5-α-reductase is absolutely crucial in this process. Therefore, it is important to conduct research on saw palmetto extracts,

which are 5-α-reductase inhibitors and can thus affect the course of the analysed process. In females the same pattern is also observed, however, the proportions and role of hormones are quite different, and here, female androgenetic alopecia (FAGA) may be more related to activity and the levels of female hormones [12,13]. Through the researcher's lens, this may diminish the role of 5-α-reductase in FAGA, while this enzyme still is very important in MAGA.

An interesting relation was examined by several clinical studies – whether AGA is related to hormone levels (both testosterone and DHT) or if is it more related to the (genetically determined) sensitivity of ARs in follicular units. The results were quite clear. The key is not the concentration of DHT (or testosterone) in the hair follicles, but the level of sensitivity of ARs in the cells of the hair follicle [14,15].

While AGA is the most frequent among alopecias, among men MAGA also shows predominance in male alopecias [16]. MAGA is a condition that is mainly driven by androgen-based perturbation of nutrient flow into the hair follicle and the upregulation of factors that speed up the hair life cycle from the anagen to the catagen phase.

Features of hair nutrition and growth mechanisms

In general, the mechanism of hair nutrition is based on the appropriate flow of micronutrients and proper levels of energy supply to all types of cells involved so that the phases of the hair life cycle, anagen, catagen and telogen, are triggered and run properly [17]. Hair, with the leading role of the hair follicle as the transporter in the process, needs a wide range of nutrients: proteins, fatty acids, and minerals [18]. Nutrient deficiencies interrupt hair growth and regrowth cycles [19]. Nutrition for hair should be covered in the field of a proper supply of protein--energy, vitamins and microelements. The key nutrients in hair growth and a proper life cycle are: vitamins (A, B-group, C, D, E) and microelements (iron, selenium, sulphur, zinc), amino acids (arginine, cysteine, glycine, histidine, l-lysine, methionine, phenylalanine) and proteins (ferritin that contains iron) [20].

The supply of nutrients is vital for the hair follicle to develop, starting from the phase of progenitor (mesenchymal) cell (induction phase), organogenesis and cytodifferentiation. On the other hand, later when a second cycle of growth is started, a hair starts to grow. Keratinocyte layers and filaments emerge and pile up on the matrix covered with dermal papilla cells (DPCs) and melanocytes on the surface of the hair follicle. Then the anagen phase, the first step in the hair life cycle, is triggered. The supply of nutrients is provided to the hair follicle to sustain the anagen phase as long as possible. Nonetheless, with the course of time, in the catagen (intermediate) phase the hair follicle seems to be shrink and slowly detach from the lower blood supply, and the nutrient flow is no longer in place. In the telogen (resting) phase, DPCs detach from the hair follicle. The exogen phase ends the life cycle of hair, when it sheds out of the head scalp [21].

The role of testosterone, and 5-α-reductase, DHT, AR in AGA

There are two principal theories on the pathogenesis of AGA. One of them recognizes the leading role of DHT, which interacts only with ARs adhering to the DPCs in the hair follicle. Another view is that AGA pathogenesis lies in the ischemic states in the head scalp, which would lead to hair loss, and consequently, the levels of testosterone, 5-α-reductase and DHT should elevate as consequence of hair loss. As the progress in this field of research shows, the latter direction has been proven wrong [14].

Testosterone is a far-backed topic of analysis regarding its impact on male sexual differentiation and functioning. Its impact on hair (growth, regrowth, life cycle, overall condition) has also been extensively studied [22]. Testosterone, along with its prohormones dehydroepiandrosterone sulfate and androstenedione, are key molecules affecting hair growth. However, as testosterone is more active towards ARs than its prohormones, DHT is 5 times more active than testosterone, whose indicator is based on the frequency of DHT adhesion to ARs in the hair follicle, compared to the same action of testosterone [23].

In the correctly working cascade of dehydrogenation, dehydroepiandrosterone is converted by another enzyme: 3-β-hydroxysteroid dehydrogenase (3βHSD) into androstenedione, which is further reformed by 17-β-hydroxysteroid dehydrogenase (17βHSD) into testosterone. Here, testosterone is converted into its '5-α-dihydroform', which is DHT, and in this reaction, only 5-α-reductase is involved as a catalyzer [24].

5-α-reductase is present in the human body and normally is expressed in two types (isoforms): type 1 and type 2. 5-α-reductase plays an important role in the development of distinctive sexual features in children, adolescents and young males. At the earliest stages of human life, 5-α-reductase catalyses the conversion of testosterone into DHT [25].

It has to be noted that there is backdoor pathway in which DHT is obtained in the reaction of androstanediol reduction by the aldo-keto reductase family 1 member C2 enzyme (AKR1C2). Nonetheless, it is of minor clinical and metabolic importance since very small amounts of DHT are generated there [26,27]. Two isoforms of 5-α-reductase are catalysers of testosterone-to-DHT conversion, but type 2 is the leading isoform since its affinity for testosterone is 10−15 times stronger than in the case of the type 1 isoform. The much less known type 3 isoform is only present in neoplastic prostate tissue and advanced prostate cancer, which means only in these clinically

pathological (abnormal) conditions [28]. Table I presents the location of both isoforms in various body regions.

Table I. Presence of 5-α-reductase isoforms 1 and 2 in various tissues (according to [24])
Tabela I. Obecność izoform 1 i 2 5-α-reduktazy w różnych tkankach (wg [24])

5-α-reductase	
type 1	**type 2**
skin transiently after birth skin permanently after puberty axillary hair follicles seminal vesicles ventral prostate	skin transiently after birth pubic and scalp skin permanently after puberty beard hair follicles

DHT has – apart from the testosterone-oriented one – a very strong affinity for ARs (a twice stronger affinity, a 5-fold lower dissociation rate than testosterone); also, it cannot be aromatized to estrogen (unlike testosterone that is converted to estrogen by cytochrome P450 aromatases). The place where DHT can be converted to a non-potent and non-androgenic form is the liver only. In this organ, 3-α-hydroxysteroid dehydrogenase (3αHSD) dehydrogenates DHT into 3-α-diol, but the scale of this metabolic pathway is very low [28]. This makes DHT, the key element in the occurrence and progression in MAGA.

Furthermore, DHT binds to androgen receptors (ARs). ARs belong to the nuclear receptor superfamily. At this stage, AR can bind either testosterone or DHT, but the latter has the strongest affinity for AR, as mentioned before. When DHT binds to AR, the heat shock protein is dissociated. Owing to this, the ligand-androgen receptor complex enters the nucleus, undergoes phosphorylation, dimerization, and further binds to androgen response elements in the promoter regions of androgen-regulated genes after co-activator recruitment, thereby affecting gene transcription. Only then the eventual form of DHT after a series of metabolic decay is chemically inactive and excreted with urine [24].

ARs are expressed in the dermal papillae of hair follicles and sebaceous glands, while they are not found in the outer root sheath, hair bulb or bulge. What has to be mentioned, ARs are very unlikely to be detected in human keratinocytes. Thus, the hair sheath is not the direct target in AGA, and the mechanism operates primarily via the dermal papillae in hair follicles [29].

The work of AR is regulated by AR coregulators, which can be divided into coactivators, integrators and repressors. In the process of binding and the further formation of a ligand-receptor complex, the most important are two coactivators: Hic-5/ARA55 and ARA70 [29].

ARA70 is expressed in two isoforms: ARA70/ELE1 and ARA70beta/ELE1beta, where the latter represents higher levels of expression and is suspected to be the most involved in the pathological chain of reactions starting from the binding of DHT to AR [30]. However, in more recent studies, the role of both isoforms is more widely explained, especially for ARA70beta/ELE1beta, which is expressed in the hair bulb and dermal papillae. When its expressions in these regions are lower, this makes ARA70beta/ELE1beta a factor responsible for the retarded growth of hair follicles; hence, hair follicle miniaturization is recognized as one of the main symptoms in MAGA [28].

Another ARs coactivator, Hic-5/ARA55, is involved in the more immediate effects of DHT-SAT (subcutaneous adipose tissue) interaction, and it is strongly suggested as a factor responsible for the elevated androgen sensitivity in the dermal papillae [29]. Thus, Hic-5/ARA55 and ARA70/ELE1 are involved in the early phase of DHT and ARs interactions, while ARA70beta/ELE1beta is more important at the later stages, when the anagen phase is destined to cease and the hair follicle is going to shrink.

Gene transcription in androgen-regulated regions results in the end of the anagen phase of hair, which on the cellular level causes them to advance to the subsequent stages of the cell cycle, where they shrink, and end their life by apoptosis. On the level of the whole hair, the hair shaft and hair follicle also shrink. Therefore, 5-α--reductase triggers the production of DHT, which on intracellular molecular pathways leads to significant shortening of the anagen phase. The action of nutrient flow disruption is not caused directly by DHT, but by the fact that the hair follicle loses its connection to lower tissues and blood vessels. This decreases access to nutrients, imminently leading to starvation of the hair follicle and hair shaft, accelerating catagen and telogen, till the phase of shedding (exogen). What is more, DHT inhibits hair regrowth, which is why the effect of balding is not only about the quickened pathway from anagen to exogen, but also the mere fact that new hair follicles do not appear in the skin [11].

5-α-reductase inhibitors

There is wide range of molecules that serve as 5-α-reductase inhibitors. They can be divided into two groups: those obtained from natural sources, and those obtained by means of chemical reactions (synthesis) [31].

Zamani et al. [31] argue that there are numerous natural inhibitors of 5-α-reductase: cedrol, cedrene, thujopsene, riboflavin, stigmasterol, β-sitosterol, 1,4-naphthoquinone, lawsone, epicatechin gallate, epigallocatechin gallate.

Iannella et al. [32] mention various classes of steroidal (synthetic) molecules that are supposedly involved in 5-α-reductase inhibition (as potential inhibitors). They are presented in Table II.

However, dutasteride and finasteride are widely proved to cause various side effects: erectile dysfunction, decreased libido, gynaecomastia, in addition to the vague and unsure effects of many classes of steroids

and their derivatives [32,33]. For this reason, attention is directed towards naturally derived 5-α-reductase inhibitors from plant sources [34].
Following this, stigmasterol, β-sitosterol, have received plenty of attention among researchers [31,34]. Both plant sterols also prove to inhibit 5-α-reductase in both AGA and prostate diseases (benign prostatic hyperplasia – BPH, prostate cancer) [35,36]. This is why, they should be studied in connection to saw palmetto extracts where they are present.

Table II. Various classes of synthesised steroidal molecules and derivatives suspected of 5-α-reductase inhibition (according to [32])
Tabela II. Różne klasy syntetyzowanych cząsteczek steroidowych i pochodnych podejrzanych o hamowanie 5-α-reduktazy (wg [32])

Azasteroids	Azasteroids derivatives	Steroidal molecules and their derivatives
2-3-azasteroids	15- and 16-azasteroids	4-substituted steroids
4-azasteroids	17- and 17a-aza-D-homosteroids	steroidal oximes
6-azasteroids	diazasteroids	steroidal tetrahydrooxazin-2-ones
7-azasteroids	11,13,15-triazasteroids	16-substituted steroids
8-azasteroids	B,D-dihomo-azasteroids	6-methylene steroidal derivatives
9-azasteroids	des-AB-azasteroids	6-methylene steroidal derivatives
19-nor-10-azasteroids	steroidal 3-carboxylic/phosphonic/phosphinic acids	derivatives of natural substrate: pregnane
11-, 12a-, 13-azasteroids	diazoketone steroids	mimics of 4-azasteroids: benzo[f]quinolinones

5-α-reductase inhibitors in saw palmetto extracts – justification for further research

Saw palmetto extract is obtained from ripe palm fruits. They contain a mixture of fatty acids (capric, caproic, caprylic, linoleic, linolenic, myristic, and oleic acid; their aggregated share in the extract composition goes up to 70−80% of the total dry mass), methyl esters, fatty alcohols (tetraconazole, hexaconazole, octacosanol, triacontanol) and phytosterols (cholesterol, campesterol, stigmasterol, β-sitosterol, and stigmastanol) [5].
Originally, sterols were not indicated as an inhibitory agent in AGA, but rather the fatty acids in saw palmetto extracts [37]. Yet later, scholars turned their attention to sterols. Wolski [38] strongly suggests that the interest in saw palmetto and based extracts should be extended, as a consequence of its high inhibitory activity against both isoforms of 5-α-reductase, compared to known steroids. Their effects are not single-dimensional as they may also produce immunomodulatory effects (the modulation of prostaglandins, leukotrienes, interleukins); additionally, it may work by stopping the cell cycle and modulating certain growth factors (epidermal growth factor – EGF, fibroblast growth factor – FGF).
There is no evidence that saw palmetto extract causes side effects similar to those coming from finasteride and dutasteride [2]. On the other hand, Evron et al. [5] reject single-sided opinions of saw palmetto extracts. Although their systematic review revealed an abundance of evidence on why this plant resource is praised, they call for more studies on the long-term effects of therapies, especially side effects. To date, only minor gastric discomfort has been revealed as a side effect of using saw palmetto as a dietary supplement against AGA [39]. Evron et al. [5] mention studies that saw the regression of MAGA in most patients to be the fastest in the few first weeks and then apparently stopped in approximately 24th week of saw palmetto extract therapy.
This is why saw palmetto extracts have to be examined by doing more research on what the detailed interactions are between their active substances and the intracellular as well as extracellular environment of hair, especially of hair follicles. Also, it has to be ascertained where the limits of using saw palmetto in AGA are, when it may produce serious side effects, or when it loses its positive therapeutical outcomes. Nonetheless, considering the fact that phytochemicals may be more promising than steroids, especially in the field of side effects, saw palmetto extracts are worth much more attention, and in-depth study may bring many satisfactory results.

Conclusions

In this study, the chain of chemical reactions involving testosterone, which is dehydrogenated to DHT by 5-α-reductase was considered. DHT is a very potent 5-α-dihydrohormone that does not involve aromatization as testosterone does, plus it has a higher affinity for ARs, which makes it the most important factor in the occurrence and progression of MAGA. The study indicates various 5-α-reductase inhibitors that exhibit therapeutical potential for balding patients. Nevertheless, there are some side effects of using such inhibitors, especially when steroids are involved.
With such a background, saw palmetto extracts may be a source of inhibitory active substances with dual values. In the first line, their value comes from the potent inhibition of 5-α-reductase action, and in the second, saw palmetto does not cause any serious side effects. The study shows that saw palmetto extracts have been verified in macroscopic studies, where the overall effects (verified by trichoscopy and other macroscopic or microscopic methods) of extract were

predominantly investigated. This may serve as an invitation for more studies with more profound approaches, where the active substances of saw palmetto (stigmasterol, β-sitosterol) are researched, or how the application of those extracts affects the hair life cycle including its various dimensions (immunological, oxidative stress, the activity of various growth factors, etc.). The study also brings attention to the fact that saw palmetto extracts are not well understood in hybrid therapies, where they are applied along with other therapeutical means.

Author's contribution

Study design – J. Pełszyńska, A. Urban, M. Piwecki
Data collection – J. Pełszyńska, M. Piwecki
Manuscript preparation – J. Pełszyńska, M. Piwecki
Literature research – J. Piwecki
Final approval of the version to be published – J. Pełszyńska, M. Piwecki, A. Urban

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