American Journal of Medicine and Medical Sciences 2014, 4(6): 262-265
DOI: 10.5923/j.ajmms.20140406.12

Minoxidil to Treat Androgenetic Alopecia in Men and Women: What is It & How does It Work?

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Abstract Androgenetic alopecia (AGA) is hereditary, progressive hair loss which advances with age and affect mostly Caucasians. AGA is androgen-dependent for both genders but can also occur without involving androgen in women. This condition also can be inherited. Androgen-dependent processes are predominantly due to the binding of dihydrotestosterone (DHT) to the androgen receptor (AR). The predisposed scalp exhibits high levels of DHT, and increased expression of the AR. Conversion of testosterone to DHT within the dermal papilla plays a central role, while androgen-regulated factors deriving from dermal papilla cells are believed to influence growth of other components of the hair follicle. Minoxidil, an anti-hypertensive agent is being the mainstay of the AGA treatment for over 30 years now. Yet, the understanding of the exact mechanism of action of this drug is still unclear. There are few hypotheses on how does this drug works to promote hair growth. The hypotheses are based on the response of hair follicles and cellular response. The inconsistencies in the results shown for hair follicle response to minoxidil mediated by its sulphate form which acts as potassium channel opener, question the evidences. Cell cultures describe a variety of response to minoxidil and some of these could promote hair growth.

Keywords Androgenetic alopecia, Hair loss, Minoxidil, Minoxidil mechanism, Androgen receptor

1. Introduction

Alopecia is a generic term for hair loss. It happens from a diminution of visible hair. [1] One of the frequent type of hair loss is androgenetic alopecia. [2] *Androgenetic alopecia* (AGA) could define as non-scaring progressive hair loss caused by miniaturization of genetically predisposed follicles. [2, 3] Male pattern of AGA is frontal recession and thinning at the vertex while female pattern is loss of hair over the crown with sparing of the frontal hair line. [1] It is also known as pattern hair loss. [4] The frequency and severity of AGA increases with age. [2] It has been reported that androgenetic alopecia affecting Caucasians [2, 3] mostly and 50% of men and women population older than 40 years. [4] Prevalence of AGA is reported lower in other ethnicity such as Asians and Africans. [2]

Action of hormones called androgens, mainly dihydrotestosterone (DHT), are involved in AGA which normally needed for normal male sexual development and have other importance in both sexes such as for libido and regulation of hair growth. [5, 6] In men, AGA is androgen-dependant along with a genetic predisposition as this condition can be inherited. [1, 2, 5] The increase in androgen can be accounted for the shedding of hair by transforming large terminal hairs in to small vellus-like hairs. [6] This is achieved by reducing size of terminal hair follicle in both length and diameter. A miniaturized vellus hair follicle is yielded by the hair bulb which moved upwards in the dermis. [3] Over time, the duration of anagen decreases as the terminal scalp hair follicles goes through progressively shorter and shorter growth cycles [3, 6] and the percentage of hair follicles in telogen increases. [1, 3] But in women, it is harder to determine if the pattern hair loss is truly androgen-dependent. [1] Shortened hair cycle and an increase in mitotic rate of matrix, telogen shedding and the duration of lag phase or catagen, stimulate DHT to induce miniaturization of hair and hair follicles. [6] The goal of treatment for hair loss should be based on the knowledge of hair shedding mechanism so that it will be effective.

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Published online at http://journal.sapub.org/ajmms

2. Content

2.1. Pathophysiology

Androgenetic alopecia is caused by a rise in central and peripheral androgen. It may also happen due to a fault in the follicle hormonal transformation occurs together with genetic predisposition. This allows the androgen to act on follicular target cells which are specifically reactive as specific intracellular androgen receptors are bind to it. The mosaic pattern in alopecia shown mostly by women is because the androgen receptors are on the X chromosomes. This also explains the reason for men involved more severely

than women. [7] AGA in general said to be an autosomal dominant gene disorder. The frequency is variable but polygenic inheritance and mutifactorial are included. [6]

Androgen receptors (AR) are required for AGA to occur. In balding scalp hair follicles AR are specific proteins called 'caspase'. The receptors will bind to 5-α-DHT. [3, 7] These hormone-receptor complexes undergo conformational changes exposing DNA binding sites and bind to specific hormone response elements (HRE) in the DNA, often in combination with accessory (coactivating) proteins, promoting expression of specific, hormone-regulated genes. [7] Then, a process called apoptosis will start. In the follicular target organ, DHT will be metabolized and transformed into 3α-androstanediolglucuronide, a DHT metabolite. This process is catalyzed by 3α-hydroxysteroid dehydrogenase enzyme. Hence, serum level of 3α-androstanediolglucuronide points to the androgenic action which causes AGA. Androgen action is complex. Testosterone, the main male circulating androgen, binds receptors in some tissues such as skeletal muscle. [7] However, in others, including secondary sexual tissues, testosterone is metabolised intracellularly by 5α-reductase enzymes to 5α-dihydrotestosterone, a more potent androgen, which binds more strongly to the androgen receptor to activate gene expression. [7]

Androgen-dependent follicles require androgen receptors to respond as highlighted by the absence of adult body hair in complete androgen insensitivity, but the need for 5α-reductase varies with body region. [7] Men with 5α-reductase type-2 deficiency only produce female pattern of pubic and axillary hair growth, although their body shapes become masculinised. [7] Therefore, 5α-dihydrotestosterone appears necessary for follicles characteristic of men, including beard, chest, and upper pubic diamond, while testosterone itself can stimulate the axilla and lower pubic triangle follicles which are also found in women. [7]

2.2. Minoxidil for Androgenetic Alopecia

Minoxidil is a pyrimidine derivative which has a chemical structure 2,4-diamino-6-piperidinipyrimidine-3-oxyde. [6] It has a very interesting history on how it was introduced as a treatment for AGA. Initially minoxidil was introduced in the early 1970's as an anti-hypertensive agent to treat hypertension. [8] It being a direct-acting arteriolar vasodilator, act specifically to open the potassium-channels. [9] Minoxidil also found to cause hypertrichosis, increase in hair growth, as a side effect in almost all patients who were treated with it throughout in the 1970s. [9] The dermatologists consider testing the oral minoxidil to treat alopecia, but considering the severe side effects it caused such as weight gain and severe water retention which need subsequent treatment with diuretic, they decided to test topical formulation of minoxidil instead. [9]

Clinical trials were carried out with 1%, 2% and 5% topical formulation of minoxidil versus placebo to test the efficacy of this drug to treat AGA in men and women. Hair growth was measured by hair counts and hair weight in the patterned hair loss areas. [4, 8] For men, 2% and 5% topical formulation is seen to be effective than 1% and placebo. [4] Actually, after further trials comparing 2% and 5% topical formulation, for men, 5% topical formulation or foam is seen to be even more effective with almost no side effects shown by any patient treated with 5% minoxidil. [9] As for women in general, 2% topical formulation is better than the placebo and safer to use than the 5% formulation. [10] This is because there was an increase in the occurrence of numerous side effects such as pruritus, local irritation, contact eczema, dryness, headaches and hypertrichosis with the use of 5% minoxidil in women. [7, 10] Recently, 1% topical solution was proven effective is Asian women. [9] But, minoxidil is not recommended for pregnant and lactating women. [7]

After a detailed observation, Food and Drugs Association (FDA) approved 2% topical solution to treat AGA in men in 1988 and for women in 1991. [2] 5% topical solution was approved by FDA to treat AGA in 1997 but only for men and same goes to 5% foam which was approved in 2006. [2]

2.3. Mechanism of Action

Minoxidil needs to be transformed into its active metabolite, minoxidilsulphate to exert its effect. [2] The conversion is done by an enzyme called sulphotranspherase which is found in the scalp. [9] According to a study, minoxidil converts to its sulphate form most likely in the lower outer root sheath. [9] Though a lot of studies are carried out, the exact process on how minoxidil actually promotes hair growth is still unclear. [2] But, there are few hypothesis on its mechanism based on researches. [9, 11] These hypothesis are divided according to the response of hair follicle and cellular response towards minoxidil. [11]

2.3.1. Response of Hair Follicle to Minoxidil

There are few ways in which a drug may promote hair growth. This includes increasing the linear growth rate of hair, increasing the diameter of the hair fibre, alter the hair cycle - either shortening telogen or prolonging anagen, or act through a combination of these effects. [11] Present evidence suggests that minoxidil acts mainly on the hair cycle. It may also increase the hair diameter. [11]

The knowledge about the effect of minoxidil in normal human hair is very little as the studies are limited mainly to the response of minoxidil for androgenetic alopecia. In men, there will be a gradual drop in duration of anagen and a prolongation of the latent periode of hair cycle, which makes miniaturized hair follicles. [11] In women, the prolongation of the latent periode is yet to be seen. [11]

According to some studies, the hair growth in both men and women is very obvious within 6-8 weeks after starting of the treatment and it peeks by 12-16 weeks of treatment. [11] The more likely explanation to this rapid response is that minoxidil stimulates follicles in latent part of telogen into anagen. Prolongation of duration of anagen in humans is supported by the increase in hair length at the forehead and

limbs seen in those treated with minoxidil orally and topically. [11] Though this is the theory, one of the researcher, Abell found that mean diameter of the hair has increased after 4 months of the treatment. But it declined after 12 months. Abell suggested that the incident is as a result of small hair recruitment into anagen. [11] Since the incident happened in the controlled groups too, the definitive theory is yet to be known.

Evidences from clinical trials suggest that, promotion of hair growth by minoxidil is related to its action as a potassium channel opener [11] because of its vasodilatory properties. Minoxidilsulphate opens the plasma membrane adenosine triphosphate (ATP)-sensitive potassium on vascular smooth muscle. [11] There was an increase in blood flow which was reputed to increase hair growth seen in diazoxide, an antihypertensice potassium channel opener. Similarly in an experiment with 16 bald men, there was an increase in cutaneous blood flow after applying 1%, 3% and 5% minoxidil solution to the scalp which occurred as soon as 15 minutes after application and lasted for approximately an hour. All three groups showed significant increase in hair growth compared to control group with greatest increase in 5% group. [9] Another group of researchers carried out organ culture studies. There is only one report found published about human hair follicle organ culture where it described about increased uptake of thymidine by cultured human hair follicles in response to minoxidil. [11] Premature entry of follicles into anagen caused by minoxidil maybe prolongs anagen and increases the size of hair follicle. [9] Most possible model by hair follicle organ culture is only prolongation of anagen. This mixed results to minoxidil most probably because of insensitivity or incapability of the model. [11] However, minoxidil does increase the life span of cultured follicles otherwise it would have degenerated rapidly *in vitro*. This sulphate metabolite mediated effect however yet to confirm the involvement of the potassium channels opening. [10] Few other researchers studied on cell culture as organ culture doesn't show enough evidence to prove the hypothesis. A group looked for potassium channels in cultured outer root sheath hair follicle and dermal papilla cells. [8] Large and small conductance calcium-activated potassium channels were identified in cell membranes. [11] The absence of K_{ATP} channels suggested by unblocked channels found in the cell membranes and unchanged ^{86}Rb efflux by minoxidilsulphate. [11]

2.3.2. Cellular Response to Minoxidil

There must be a primary effect on cell function whatever mechanism it is for minoxidil to stimulate hair growth. [11] Regulation of epithelial growth and differentiation and the hair cycle involving interections between cells of hair follicle. [11] Studies on mouse showed that minoxidil and minoxidilsulphate concentrated in melanocytes and pigmented epithelial cells in the suprapapillary region of the follicle. [11]

A study on the effect of minoxidil on human keratinocytes of epidermal and hair follicle origin using different culture conditions and proliferative markers found that, micromolar concentrations of minoxidil promotes proliferation in both cell types and cultured conditions. However, millimolar concentrations inhibited cell growth. [11] Another study by different group also failed to prove that minoxidil in cultured human epidermal keratinocytes shows a stimulatory response. [11] Similarly, studies using fibroblasts showed variable results. It was reported that, the growth of human skin fibroblasts can be inhibited by high concentration of minoxidil. [11] There were two morphologically distinct cell types, suggesting that minoxidil can affect epidermal cells in culture by altering their growth pattern and phenotypic appearance. [9] It is difficult to compare the results from the studies as there are variations. On the safe side, it can be said that minoxidil slows the senescence of keratinocytes and reduces the rate of which cells are lost from germinative pool. [9]

Activity of purified ovine PGHS-1 *in vitro* and synthesis of PGE_2 by cultured human dermal papilla are stimulated by minoxidil. [11] It is also found that minoxidil inhibited production of prostacyclin by dermal papilla cells, measured as 6-keto-prostaglandin $F_{1\alpha}$ as bovine endothelial cells were used in an earlier study. [11]

VEGF promotes angiogenesis and influence diverse cell functions mainly. [11] The perifollicular capillary network together with hair cycle, increase during anagen and then decrease during catagen and telogen which was found temporary and associated spatially with the VEGF in the outer root sheath. [11] This transgenic overexpression in return accelerates the hair growth after depilation and the larger hair growth. A group reported recently that minoxidilupregulates the expression of vascular endothelial growth factor mRNA in human hair dermal papilla cells. [9] Another group of researchers found another possible mechanism of minoxidil stimulation of VEGF. Adenosine is found to increase VEGF release and the pharmacological blackade of A1 and A2 receptors prevented the VEGF response to minoxidil. [11] Reverse transcriptase–polymera se chain reaction detected mRNAs for the A1, A2A and A2B adenosine receptors, as well as the sulphonylurea receptor SUR2B. The authors suggested that binding of minoxidil to SUR2B promotes secretion of ATP, which is rapidly converted to adenosine and activates adenosine signalling pathways. [11]

3. Conclusions

Androgenetic alopecia is non-scarring hair loss condition which advances with age. So far, it has been affecting Caucasians more than any other ethnics in the world. There is definitely androgen action in androgenetic alopecia in men along with genetic predisposition. But, it can be androgen-dependent or androgen-independent and it can be inherited for women. The genetics involved in androgenetic alopecia is complex. It is said because it is an autosomal

dominant gene disorder with variable regularity. The emergence of topical minoxidil as a treatment for androgenetic alopecia gave hope to the society that this condition is treatable. Though the drug was introduced as an antihypertensive agent about 30 years ago, the side effects from this drug to those treated for hypertension ushered a new era in hair research. The FDA approved 2% and 5% topical solution and 5% foam for men. However, 2% topical solution is the only FDA approved treatment for women as the higher concentrations causes severe side effects such as local irritation and pruritis.

The action of minoxidil is stronger in minoxidilsulphate form. Though the assumption is it works through potassium channel opening, the knowledge about the exact process of how minoxidil stimulates hair growth is very limited. There are many hypotheses but the mechanism is still unclear. There are suggestions that hair follicle response to minoxidil is mediated by minoxidilsulphate being a direct-acting vasodilator to open the potassium channel. But, evidence shown about this theory is inconsistent. A variety of responses to minoxidil have been described in cell cultures. Some actually are relevant to stimulate hair growth such as in cell growth and delay in aging and also the stimulation of VEGF and prostaglandin synthesis. Although the benefits in androgenetic alopecia have been demonstrated in clinical trials, there is perhaps a tendency to dismiss the significance of minoxidil. Yet, it remains the only medical treatment of proven efficacy when used topically. Minoxidil affects hair cycle, causing premature termination of telogen and probably prolonging anagen. Understanding how minoxidil exerts these effects may lead not only to better treatments for hair loss but also will increase our understanding of the mechanisms responsible for controlling the hair cycle.

ACKNOWLEDGEMENTS

First of all, I would like to show my gratitude to the Almighty because I have managed to complete this paper on Minoxidil to Treat Androgenetic Alopecia in Men and Women: What is it & How does it Work, with his blessings.

With pleasure, I, **Theanmulllai Palanisamy**, would like to convey my heartiest thank you to **Dr. I Wayan Sugiritama**, **M. Kes**, supervisor for my paper work whose encouragement, guidance, and support from the initial to the final level enabled me to develop an understanding of the topic and successfully complete it.I would also like to extend my gratitude to **Dr. I. G. A. Dewi Ratnayanti**, **M. Biomed**, for the support.

I would like to apologize if there are any weaknesses that could be found in my report and I would be glad to get feedbacks from the readers as it would help me in improvising myself in time to come. Last but not least, I hope that my writing would be beneficial to the readers as how it was to me.

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