Minoxidil: What It Is and How It Works

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Minoxidil is a piperidine-pyrimidine derivative and a potent vasodilator approved orally for severe hypertension and topically for androgenetic alopecia (AGA).[1] The minimum plasma threshold for induction of hair growth is an order of magnitude below the threshold required for any hemodynamic effect.[2,3]

With respect to its hemodynamic effects, oral minoxidil (OM) is a pro-drug converted by hepatic dehydroepiandosterone sulfotransferase (SULT2A1) into minoxidil sulfate.[4] Heterogeneity in the efficiency of SULT2A1 activity influences its antihypertensive efficacy.[5] There are many mammalian SULT isoforms that differ in tissue expression and substrate selectivity.[6] OM is well absorbed through the gastrointestinal system (>90%). Oral doses of 2.5mg and 5mg of minoxidil provide peak plasma concentrations (CMAX) of 18.5 and 41ng/mL, respectively, one-hour post-dose.[7] OM in doses of 5mg to 100mg daily produces a dose-dependent reduction in blood pressure (BP) in hypertensive patients but has minimal effect on the BP of normotensive individuals.[8] Reflex tachycardia and sodium retention can occur.[9] The plasma concentration threshold of minoxidil for any hemodynamic response is 18ng/ml.[2]

With respect to hair growth, minoxidil is also a pro-drug converted by follicular thermostable phenol sulfotransferase (SULT1A1) into minoxidil sulfate.[10-12] There is considerable inter-subject variability in follicular SULT1A1 and low SULT1A1 predicts a weak response to minoxidil.[13,14]

Minoxidil is poorly soluble. The maximum concentration stable in solution is 5% (50mg/ml). Percutaneous absorption ranges between 1.5-4%.[15] Mean CMAX after twice daily application of 2% minoxidil lotion (20mg/ml) is 0.7ng/ml and 1.8ng/ml with 5% minoxidil (50mg/ml). Application frequency higher than twice daily does not further increase absorption as the initial dose saturates the skin for a period of time longer than the dosing interval.[3] Patients in whom maximal minoxidil therapy produces sub-therapeutic plasma levels will not respond to minoxidil.

Minoxidil lotion is considered to be a topical therapy; however, the demonstration that OM produces dose-dependent hair growth and that OM used in doses that produces similar serum levels to minoxidil produces equivalent hair regrowth suggest that minoxidil is in fact a systemic therapy with a transdermal delivery mechanism.[16]

This is supported by the following findings:

1. Follicular SULT1A1 (and not hepatic SULT2A1) bio-activates both OM and minoxidil and predicts hair growth response.[11,14,17]
2. SULT1A1 expression is restricted to the keratogenous zone of the hair bulb.[10,12] minoxidil promotes growth of both terminal and vellus hairs, but terminal anagen bulbs are mostly located in the subcutis, inaccessible to topical therapies.[18]
3. The observations of distant hypertrichosis in patients who apply minoxidil to the scalp[19] and that the pattern and distribution of hair regrowth seen with oral minoxidil is the same as that seen with minoxidil lotion.[20,21]

Hair formation occurs as a two-stage process. In the first stage, hard α keratin intermediate filaments assemble to form a cytoskeleton.[22] The second stage involves the synthesis of cysteine rich interfilamentous keratin-associated proteins (KAPs) that form the matrix in the keratinized hair cortex.[23] The SULT1A1 enzyme is juxtaposed with the second stage of fibre synthesis, but its function is unknown in the absence of minoxidil treatment.

Cysteine is an essential prerequisite for the second stage of hair growth[22,23] and cysteine availability is the rate limiting step for fibre formation.[23,24] Minoxidil sulfate is 14 times more potent than minoxidil in stimulating cysteine incorporation into the keratogenous zone of the follicle above the dermal papilla.[25] Cysteine has a role in determining fibre diameter and linear growth rate[24,26,27] and is also involved in the synthesis of glutathione and coenzyme A that increase and induce epithelial cell proliferation in the bulb.[23]

Cysteine is actively transported into the follicle by the Alanine/serine/cysteine/threonine transporter 1 (ASCT1), a sodium-dependent, neutral amino acid transporter, expressed in the outer root sheath and hair cortex of the keratogenous zone of the bulb.[28-30] Expression of both ASCT1 and SULT1A1 is restricted to the keratogenous zone of the bulb. ASCT1 enables uptake of cysteine in the blood supply against the concentration gradient.[28-30] Minoxidil also binds to SUR2 sulfonylurea receptors on the KATP channels in the dermal papilla, stimulating them to open[31] and directly activates prostaglandin endoperoxide synthase-1 (PGHS-1) in the dermal papilla. PGHS-1 is cytoprotective and promotes hair growth through increased production of PGE2.[32,33] The relative contribution of these actions to hair growth is unknown.

Approximately 50% of the population has low SULT1A1 activity and overall approximately 50% of patients treated with minoxidil fail to achieve any regrowth.[11,18] Increasing the concentration of minoxidil lotion or the frequency of application does not increase regrowth due its low solubility, poor percutaneous absorption, and saturation absorption kinetics. Maximal minoxidil therapy may be sub-therapeutic in patients with low SULT1A1, and minoxidil non-responders generally require systemic administration of minoxidil for hair growth.

OM produces dose-dependent hair growth even in patients with low SULT1A1 activity.[21] OM undergoes first-pass hepatic metabolism to minoxidil sulfate by SULT 2A1, simultaneously increasing the risk of hemodynamic side effects and reducing hair follicle bioavailability of minoxidil. Minoxidil sulfate is only stable in the circulation for a maximum of 30 minutes and diffuses poorly from the circulation into the skin due to its higher molecular weight.[34] There is no known correlation between SULTs1A1 and 2A1 activity.

We have investigated sublingual minoxidil as an alternative to OM.[34] Sublingual dosing bypasses hepatic first pass metabolism and therefore might be expected to increase the follicular minoxidil sulfate bioavailability and consequently hair growth.[34] As hepatic sulfation of minoxidil enhances the hemodynamic effect, sublingual dosing might also reduce the risks of postural hypertension, fluid retention, and tachycardia. We anticipate publishing additional results from our sublingual minoxidil trials in the near future.

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