Estrogens and Human Scalp Hair Growth—Still More Questions than Answers

To the Editor:

While it is undisputed that estrogens (17-β-estradiol, E2) can profoundly modulate hair growth in practically all mammalian species investigated, usually exhibiting hair growth inhibitory properties (Emmens, 1942; Williams et al., 1946; Stumpf et al., 1974; Ebling et al., 1991; Smart et al., 1999; Chanda et al., 2000), it is still rather unclear what exactly E2 administration does to human scalp hair growth.

Given the profound clinical relevance of this question and the frequent use of E2-containing topical preparations in trichological practise (Sinclair, 1999; Sterry and Paus, 2000), this question deserves a more careful and more systematic dissection than it has experienced in the past. This letter calls attention to a few salient points that should be taken into account in this respect.

For human scalp hair, topical E2 has long been used in the management of telogen effluvium and androgenetic alopecia, especially in women (Wüstner and Orfanos, 1974; Schuhmacher-Stock, 1981; Sterry and Paus, 2000). Even though this remains to be unequivocally proven in vivo, it is felt that E2 inhibits hair shaft formation, thus lowering the rate of hair growth, i.e., how much new hair shaft is generated by the anagen hair bulb per time unit, yet prolongs anagen duration, thus decreasing the telogen rate (Schuhmacher-Stock, 1981; Sinclair et al., 1999). This would help to explain the clinical observation that topical E2 or high systemic E2 levels during estrogen-based contraception and during pregnancy increase the telogen/anagen ratio, thus notably improving a pre-existing telogen effluvium, while causing a telogen effluvium postpartum supposedly due to E2 withdrawal (Lynfield, 1960; Barman et al., 1969; Ebling et al., 1991). In view of the very complex, multiple concomitant endocrine changes during and after pregnancy and lactation (including, e.g., dramatic fluctuations in gestagen and prolactin levels (Braunstein, 2003)), it is however exceedingly difficult to dissociate strictly E2-based hair growth effects from those that other hormones might exert on the human scalp hair follicle in vivo during this time.

Therefore, it is reasonable to explore the isolated effects of E2 on human hair shaft elongation, anagen duration, and hair follicle keratinocyte proliferation/apoptosis in microdissected human anagen VI scalp hair follicles that are organ-cultured according to the method pioneered by Philpott et al. (1990)—in the absence of the sebaceous gland, a key compartment for steroid hormone synthesis and metabolism (Zouboulis, 2000). We found only two corresponding reports in the published literature, one using human anagen hair follicles from an unspecified scalp skin location of what appears to be two male individuals aged 17 and 35 y (Kondo et al., 1990), and one recent meeting abstract based on the use of female occipital scalp skin follicles (Nelson et al., 2003). Both studies report that E2 (Kondo et al.: 18 nM; Nelson et al.: 10 nM), significantly inhibits human scalp hair shaft elongation in vitro. In addition, Kondo et al. (1990) report that E2 does not influence the “decay rate” of organ-cultured human anagen hair follicles (as measured by morphology and autoradiographic 3H-thymidine incorporation).

Recently, we have also studied the effects of E2 (1 nM–1 μM, Sigma St. Louis, MO) on female occipital scalp hair follicles, and have essentially confirmed hair shaft elongation-inhibitory properties of E2, which were maximal at 1 μM (Ohnemus et al., 2003). In view of the extreme dependence of androgen effects on the exact integumental location of human hair follicles however (Ebling, 1991; Jahoda and Reynolds, 1996), we were curious to learn whether E2 effects on human scalp hair follicles are location- and/or sex-dependent. This has already been demonstrated for the E2 response of pelage hair follicles from mice and rats, which is profoundly influenced by sex and body site (Emmens, 1942; Mohn, 1958).

Therefore, we have investigated in a single, large, frontotemporal scalp skin sample (healthy male individual, no medications, 46 y; obtained with informed consent during routine facelift plastic surgery; all experiments were performed in order to the Declaration of Helsinki Principles) how E2 addition to the medium (1–100 nM, Sigma, diluted in serum-free William’s E medium, supplemented with l-glutamine, penicillin, streptomycin, insulin, and hydrocortisone) affected hair shaft elongation, anagen duration, hair follicle pigmentation and hair matrix keratinocyte proliferation in microdissected, organ-cultured male anagen VI hair follicles from the frontotemporal scalp skin region.

Surprisingly, compared to the vehicle control, the hair shaft elongation of male frontotemporal scalp hair follicles was significantly stimulated by 1–100 nM E2 already as early as 1 d after the start of organ culture, and this stimulation became even more pronounced at the end of organ culture (days 7 and 9) (Fig 1). This stimulation of hair shaft formation (which is the result of stringently coordinated proliferation and differentiation of hair matrix keratinocytes (Stenn and Paus, 2001) corresponded to a significant stimulation of hair matrix keratinocyte proliferation by 10 nM E2 at day 9 (average number of Ki-positive-cells: in the control group 14 cells (SEM 3.21) and 26 cells in the E2-treated (10 nM) group (SEM 4.38); level of significance: p<0.05, Mann–Whitney test). While no evident differences were noted by H&E or

Abbreviations: E2, 17-β-estradiol; ER, estrogen receptor; ER-α, estrogen receptor type alpha; ER-β, estrogen receptor type beta.
much more systematically by subsequent work on the effects of E$_2$ on human hair growth in order to better explain the seemingly contradictory results obtained with occipital (Kondo et al., 1990; Nelson et al., 2003) versus frontotemporal scalp hair follicles (Fig 1):

1. What are the differences between male and female hair follicles with respect to estrogen receptor (ER-$
\alpha$, ER-$
\beta$) expression (Thornton, 2003) and aromatase activity (Sawaya and Price, 1997; Hoffmann, 2001, 2002)?

2. How do occipital and frontotemporal hair follicles, as well as various other integumental sites, differ from each other in this respect?

3. Is there any indication that E$_2$ exerts similarly “paradoxical, site-dependent” effects on human hair growth as androgens (Jahoda and Reynolds, 1996)? Does the signalling and gene expression response of a defined human hair follicle population to E$_2$ stimulation differ in a stringently location-dependent manner, as has been postulated, e.g., for the response of beard hair versus scalp follicles to androgen stimulation with respect to TGF$eta$1 expression in the dermal papilla (Inui et al., 2002)?

4. Which important regional differences in the extrafollicular estrogen metabolism of defined integumental sites must be taken into account when estrogens are administered topically (e.g., with respect to epidermal, sebaceous, and dermal activities of key enzymes like aromatase, 17$
\beta$-hydroxysteroid dehydrogenase, or steroid sulfatase)?

5. How is ER expression and/or the metabolism of topically applied estrogens in loco influenced by the choice of vehicle?

Only when these basic questions are finally addressed systematically can we expect to solve the ancient enigma of what estrogens really do to human hair growth in a defined integumental site in vivo, on the scalp and elsewhere, and can rationally select estrogen receptor ligands for therapeutically desired hair growth modulation.

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References


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*Note added in proof: The stimulation of male frontotemporal hair follicles by E$_2$ reported here (Fig 1) was just confirmed by us using frontotemporal hair follicles from a second male patient.


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