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REVIEW ARTICLE

Oxidative stress and its impact on skin, scalp and hair

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Abstract

Oxidative stress is an unbalanced condition in which the tissues of the body are not sufficiently able to counteract either exogenous or endogenous sources of reactive oxygen species. Oxidative stress is strongly associated with ageing, both local and systemic, as well as a wide range of local health conditions. This review focuses on the oxidative stress data known for skin, scalp and hair. This oxidative stress may be the 'currency' by which an unhealthy scalp leads to deleterious consequences to the hair. The ramifications of this scalp oxidative stress to normal hair elongation, retention and replacement are discussed.

KEYWORDS

hair growth, hair loss, hair treatment, oxidative stress, skin barrier

Résumé

Le stress oxydatif est une condition déséquilibrée dans laquelle les tissus du corps ne sont pas suffisamment capables de contrer la source exogène ou endogène d'espèces réactives de l'oxygène. Le stress oxydatif est fortement associé au vieillissement, à la fois local et systémique, ainsi qu'à un large éventail de problèmes de santé locaux. Cette revue se concentre sur les données de stress oxydatif connues pour la peau, le cuir chevelu et les cheveux. Ce stress oxydatif peut être la « devise » par laquelle un cuir chevelu malsain entraîne des conséquences délétères pour les cheveux. Les ramifications de ce stress oxydatif du cuir chevelu sur l'allongement, la rétention et le remplacement normaux des cheveux sont discutées.

INTRODUCTION

Hair care, colour and style play an important role in people's overall physical appearance and self-perception. Hair defines an individual's gender, sexual attitude and social status. Eventually, ageing of the hair is particularly visible. And yet, the care of the ageing hair has found lesser attention than the skin for a number of reasons. First, the market for facial rejuvenation has been dominated by plastic surgeons, until the fillers and botulinum toxin were introduced. Second, investigative dermatology found a profound interest in the study of skin ageing, particularly as it relates to ultraviolet exposure, and exposed mechanisms at the level of the DNA and repair mechanisms, opening venues for effective preventive measures and pharmacological treatments of ageing-related conditions of the skin. Finally, at the level of health professionals, the care for the skin has been overrated in relation to the hair, mostly due to economic reasons [1].

Skin ageing is caused by intrinsic and extrinsic mechanisms. Intrinsic skin ageing represents the normal course of ageing for all tissues, whereas extrinsic ageing is mainly caused by exposure to UV radiation, pollution

and cigarette smoking that is superimposed on intrinsic or chronological skin ageing. Exposed areas of the body such as the face are, therefore, subjected to both types of skin ageing.

Ageing of the scalp underlies the same principles as ageing of the skin, except for a natural protection from UVR depending on the amount of scalp hair. Ageing represents the accumulation of changes over time, involving both programmed factors and damage-related factors (non-programmed factors). Programmed factors follow a biological timetable, perhaps a continuation of the one that regulates childhood growth and development. This regulation would depend on changes in gene expression that affects the systems responsible for maintenance, repair and defence responses. Damage-related factors include internal and environmental assaults that induce cumulative damage at various levels.

Ageing of the hair affects hair colour (greying), hair production (alopecia) and structural properties of the hair fibre (hair diameter, hair fibre curvature, stretching, bending and torsional rigidity of the hair fibre, and lipid composition) with its consequence for the manageability and overall appearance of hair [2].

Ultimately, basic scientists interested in the biology of hair growth and pigmentation have exposed the hair follicle as a highly accessible model with unique opportunities for the study of the age-related effects [3] with a special focus on the role of oxidative stress.

THE FREE RADICAL THEORY OF GREYING

Experimental evidence supports the hypothesis that oxidative stress plays a major role in the ageing process. In 1956, Harman et al. [4] originally proposed the free radical theory of ageing. Free radicals are highly reactive molecules with unpaired electrons that can directly damage various cellular structural membranes, lipids, proteins and DNA. The damaging effects of these reactive oxygen species are induced internally during normal metabolism and externally through exposure to various oxidative stresses from the environment. While the body possesses endogenous defence mechanisms, such as anti-oxidative enzymes (superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic anti-oxidative molecules (vitamin E, vitamin C, glutathione, ubiquinone), to protect it from free radicals by reducing and neutralizing them, with age, the production of free radicals increases, while the endogenous defence mechanisms decrease. This imbalance leads to the progressive damage of cellular structures, presumably resulting in the ageing phenotype.

By analogy to Harman's original free radical theory of ageing, Arck et al proposed a free radical theory of greying [5]: the extraordinary melanogenic activity of pigmented bulbar melanocytes, continuing for up to 10 years in some hair follicles, is likely to generate large amounts of reactive oxygen species via the hydroxylation of tyrosine and the oxidation of DOPA to melanin. Tobin [6] has reviewed the sometimes dichotomous data regarding the causative role of oxidative stress in hair greying. The highly ROS-generating nature of melanogenesis can be confounding with respect to why such a process could then be inhibited by these very products of the normal process. If not adequately removed by an efficient antioxidant system, an accumulation of these reactive oxidative species will generate significant oxidative stress. There are data indicating that the natural ability of the body to counteract oxidative stress declines with advancing age [7, 8]. Thus, while normal melanogenesis produces significant ROS, it is the declining ability of the body to counteract this with age that eventually inhibits the process.

Since the discovery of unpigmented melanocyte stem cells located within the hair follicle by Nishimura et al [9], the question arose whether the process underlying hair greying arises from changes in differentiated, pigmented melanocytes or the unpigmented progenitors which provides them. Utilizing melanocyte-tagged transgenic mice and ageing human hair follicles, Nishimura et al. [10] demonstrated that hair greying is caused by defective self-maintenance of melanocyte stem cells, and not of differentiated melanocytes.

ROLE OF OXIDATIVE STRESS IN HAIR GROWTH AND AGEING

Androgenetic alopecia is the single most frequent cause of hair loss in men and women that is traditionally understood to represent a genetically determined, androgen-induced and age-dependent progressive loss of hair with sex-dependent differences in incidence, pattern and severity.

Meanwhile, an alternative definition is evolving of a genetically determined, organ-specific (hair follicle) premature ageing process with an increased sensitivity to internal and external factors: hormonal, environmental, inflammatory, vascular and dietary [11].

Bahta et al. [12] cultured dermal hair papilla cells (DPC) from balding and non-balding scalp and demonstrated that balding DPCs grow slower in vitro than non-balding DPCs. Loss of proliferative capacity of balding DPCs was associated with changes in cell morphology, expression of senescence-associated beta-galactosidase, decreased expression of proliferating cell nuclear antigen

and Bmi-1, upregulation of p16(INK4a)/pRb and nuclear expression of markers of oxidative stress and DNA damage including heat-shock protein-27, superoxide dismutase catalase, ataxia-telangiectasia-mutated kinase (ATM) and ATM- and Rad3-related protein. The finding of premature senescence of balding DPC in vitro in association with the expression of markers of oxidative stress and DNA damage suggests that balding DPCs are particularly sensitive to environmental stress.

Upton et al [13] further investigated the effects of oxidative stress on balding and occipital scalp DPCs. Patient-matched DPCs from balding and occipital scalp were cultured at atmospheric (21%) or physiologically normal (2%) O2. At 21% O2, DPCs showed flattened morphology and a significant reduction in mobility, population doubling, increased levels of reactive oxygen species and senescence-associated β-Gal activity, and increased expression of p16(INK4a) and pRB. Balding DPCs secreted higher levels of the negative hair growth regulators TGF beta 1 and 2 in response to H2O2 but not cell culture-associated oxidative stress. Balding DPCs had higher levels of catalase and total glutathione but appeared to be less able to handle oxidative stress compared with occipital DPCs. These in vitro findings suggest that there may be a role for oxidative stress in the pathogenesis of androgenetic alopecia, in relation to both cell senescence and migration, but also secretion of known hair follicle inhibitory factors, at the same time offering new opportunities for treatment of androgenetic alopecia beyond minoxidil and the 5alpha-reductase inhibitors.

Finally, Nishimura et al [14] revealed that mammalian hair follicles miniaturize and often disappear from the skin in the course of ageing through defective renewal of hair follicle stem cells much in the same manner as maintenance of melanocyte stem cells becomes incomplete with ageing. Hair production is fuelled by stem cells, which transition between cyclical bouts of rest and activity. Aged hair follicle stem cells exhibit enhanced resting and abbreviated growth phases and are delayed in response to tissue-regenerating cues. Ultimately, aged hair follicle stem cells are poor at initiating proliferation and show diminished self-renewing capacity upon extensive use. Ageing-related loss of hair follicle stem cell marker expression starts well before hair follicles have shortened. Using genomic instability syndromes and exposure to ionizing radiation as models, Nishimura proposed an accumulation of DNA damage to be involved in the ageing process [15]. Further, Nishimura et al [14] found that hair follicle stem cell ageing resulted from proteolysis of type XVII collagen (COL17A1/BP180) by protease expression in response to DNA damage in stem cells and their commitment to epidermal differentiation. This enables the transepidermal elimination of damaged stem cells as shed corneocytes from the skin surface.

ROLE OF OXIDATIVE STRESS IN SCALP HEALTH AND DISEASE

The scalp is characterized by a usually high density of terminal hair growth with numerous sebaceous glands that contribute to a specific microenvironment with significant differences from the rest of the skin. The scalp is a rich environment for microbes. Ecologically, sebaceous areas have greater species richness than dry ones, with implications for both skin physiology and pathologic conditions [16].

Traditionally, the study of hair care has focused on two main streams of attention: on the one hand, the aesthetic problem of the condition of the hair fibre in terms of hair quality and colour and on the other hand, the underlying problem of hair ageing and pathologies.

The condition of the hair fibre must be viewed as the result of a combination of pre-emergent and of post-emergent factors [17]. Sources of oxidative stress with impact on the pre-emergent fibre include the following: oxidative metabolism, smoking [18], UVR [19], inflammation from microbial, pollutant or irritant origins and oxidized scalp lipids. Sources of oxidative stress with impact on the post-emergent fibre include the following: again UVR and chemical insults from oxidizing hair colourants and pollutants [20].

Naito et al. [21] analysed the effect of the lipid peroxides on murine hair follicles and observed that the topical application of linolein hydroperoxides, one of the lipid peroxides, leads to the early onset of the catagen phase in murine hair cycles. Furthermore, they found that lipid peroxides induced apoptosis of hair follicle cells. They also induced apoptosis in human epidermal keratinocytes by up-regulating apoptosis-related genes. These results indicate that lipid peroxides, which can cause free radicals, induce the apoptosis of hair follicle cells, and this is followed by early onset of the catagen phase.

Since free radical-mediated lipid peroxidation has been implicated in human disease, methods have been developed to measure lipid peroxidation products as potential biomarkers of oxidative stress. The biomarkers are used for health examination, diagnosis of pathologic processes and evaluation of the effects of drugs and cosmetics. Since lipid peroxidation product can be measured more quantitatively than the oxidatively modified proteins and DNA, levels of lipid oxidation products have been widely accepted as a biomarker of oxidative stress and measured extensively for healthy subjects and diseased patients. Specifically, lipid hydroxides such as hydroxyoctadecadienoic acids

(HODE) are recommended as reliable markers as measured by liquid chromatography and mass spectrometry (LC-MS/MS). Substantial evidence shows the association between the level of these biomarkers and development of disease conditions [22, 23].

Dandruff and seborrheic dermatitis, psoriasis, atopic dermatitis and ultimately alopecia represent pathologic conditions in which oxidative stress is very commonly detected [24].

Ultimately, the oxidized lipids are understood to negatively influence the normal growth of hair. Specifically, in the context of scalp condition and its impact on the pre-emergent hair and ageing, *Malassezia* is a proven source of oxidative stress [25, 26], with a correlation between *Malassezia* presence and the degree of oxidative stress [27, 28].

THE EFFECT OF SCALP CARE ON HAIR GROWTH AND QUALITY

Remarkably, ageing does not appear to follow a perfectly regular course over time. Periods of stability, or even partial remission, alternated with periods of more marked evolution, reflecting perhaps the influence of individual factors such as the subject's general health and nutritional status, lifestyle, hygiene, and risk... factors for accelerated ageing.

There is increasing evidence from data involving collections and characterization of hair samples from various unhealthy scalp conditions to help establish a link between scalp condition and hair growth and quality [29]. A number of observations have found that premature hair loss may be caused by poor scalp condition associated with oxidative stress such as psoriasis [30–32] and dandruff/seborrheic dermatitis [32–35]. The effect on the pre-emergent hair fibre may alter the anchoring force of the fibre with the follicle, as evidenced by an increased proportion both of catagen and telogen [32] and of dysplastic anagen hairs (anagen hairs devoid of hair root sheaths) [36, 37] in the trichogram (hair pluck) of scalp pathologies, such as dandruff, seborrheic dermatitis and psoriasis.

Despite Gan et al.'s observation of a significant positive association between the presence of grey hair and history of dandruff, this was without a statistical relationship between clinical grades of greying and dandruff in males [38].

Psoriasis and dandruff/seborrheic dermatitis are associated with abnormally high levels of *Malassezia* yeasts [39, 40]. *Malassezia* metabolism produces ROS [28]. Oxidative stress, the inability of the body to sufficiently counteract sources of oxidative damage, is prevalent in all of these skin conditions, just as in normal skin ageing. Considering the relationship between oxidative stress, *Malassezia* spp., scalp pathologies and hair ageing, it is therefore conceivable that the use of *Malassezia*-control products will reduce oxidative stress.

Finally, nutraceuticals on the basis of antioxidants have as yet to be studied with respect to their efficacy in the specific perspective of ageing-related changes in hair growth and quality. Although some antioxidants have shown substantive efficacy in cell culture systems, unequivocal confirmation of their beneficial effects in human populations has so far proven elusive [24].

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