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The hair eclipse phenomenon: sharpening the focus on the hair cycle chronobiology

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Synopsis

Chronobiology governing the hair cycle is a fascinating and complex process. Both the hair growth cycle and the hair shaft growth are coordinated and depend on the interplay of different biological signals and various exogenous stimuli. A latency period may occur between hair shedding (teloptosis, exogen phase) and the early emergence of the next anagen VI stage. This lag time referred to on the hair eclipse phenomenon likely depends on the influence of a series of distinct synchronizers, and does not represent *per se* a peculiar hair cycle phase. It is the result of some dysregulations of the hair cycling, involving early teloptosis, delayed anagen I initiation or stunted hair growth at any stage between the anagen I and anagen V phases. As such, the hair eclipse phenomenon may be an erratic process occurring in physiopathological conditions affecting hair follicles singly or in focal to generalized patterns. It may be more frequent when it follows synchronized teloptosis occurring in telogen effluvium (newborn alopecia, post-partum alopecia, seasonal alopecia and alopecia areata). It may also be prominent when microinflammation is abutted on the permanent portion of the hair follicle as in dandruff, seborrhoeic dermatitis, androgenic alopecia and photoageing baldness. Local synchronizers such as growth factors and other mediators may eventually be lacking or involved in the hair eclipse phenomenon. Their identification and characterization might drive new corrective or preventive applications.

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Résumé

La chronobiologie à la source du cycle pilaire est un processus à la fois complexe et fascinant. Le cycle pilaire et la croissance pilaire sont coordonnés et dépendent de l'interaction de divers signaux biologiques et stimuli exogènes. Un temps de latence peut survenir entre la chute du cheveu (téloptose, phase 'exogène') et l'émergence du cheveu suivant en stade anagène VI. Cette période correspondant au phénomène d'éclipse pilaire est sous l'influence probable d'un ensemble de synchronisateurs distincts et ne représente pas en tant que tel une phase particulière du cycle pilaire. Ce phénomène serait en fait le résultat de dérégulations du cycle pilaire impliquant une téloptose précoce, un retard d'initiation du stade anagène I, ou un arrêt transitoire de croissance pilaire à n'importe quel moment entre les stades anagènes I et V. Le phénomène d'éclipse pilaire peut donc être un processus erratique survenant dans diverses situations physiopathologiques atteignant des follicules pileux isolés, groupés focalement ou dispersés de manière généralisée. Il peut être plus fréquent à la suite d'une téloptose synchronisée à l'origine d'un effluvium télogène (alopécie du nouveau-né, alopécie du postpartum, aloépcie saisonnière, pelade). Le phénomène d'éclipse pilaire peut égalemnet être important lorsqu'une microinflammation entoure la portion permanente du follicule pileux. Tel est le cas dans les états pelliculaires, la dermite séborrhéique, l'alopécie androgénétique et l'alopécie du photovieillissement. Des synchronisateurs locaux tels que des facteurs de croissance et d'autres médiateurs pourraient être déficients ou au contraire être impliqués dans le phénomène d'éclipse pilaire. Leur identification et caractérisation

pourraient aboutir à des applications à visée corrective ou préventive.

Introduction

The field of hair growth treatment has deservedly earned for years a notorious reputation based on false claims for treating baldness. Truly effective means must affect the regulation of hair follicle growth and thus some synchronizers of this aspect of chronobiology. Presently, most of the mechanistic conclusions about the specific pathways and molecules involved in hair cycling are only based on time-related associations between growth control factors in and about the cycling follicle.

Hair growth involves the unique phenomenon of cyclic regeneration [1]. The anagen, catagen and telogen phases follow each other over a recurrent period closely controlled by chronobiological synchronizers. The extended anagen phase is characterized by massive cell proliferation and terminal differentiation and involves epithelial growth of the hair follicle into the dermis with regeneration of the hair shaft. The catagen phase is induced with rapid involution of the hair follicle and proceeds to the telogen phase of follicular quiescence that awaits the next signals for anagen initiation.

Chronobiology of hair cycling

The chronobiological control system that cyclically drives the hair follicle through dramatic remodelling processes remains largely putative. Controls of the onset, duration and speed of each phase of the hair cycle are indeed complex. They involve a series of synchronizers, which may be concomitantly up- or downregulated for sustaining hair growth and for moving from one stage in the hair cycle to the next [1–4]. At the end of telogen phase, the hair shaft is loosely anchored to the outer root sheath and may fall spontaneously or be simply removed by gentle combing or washing. It is also believed to be pushed out as a new anagen VI hair emerges. Teloptosis or exogen phase are the terms describing the shedding time of the club hair [5–7].

During follicle cycling, changes appear in associated cells and structures that might influence the cycle. They include vessels, lymphocytes and basement membranes, as well as the epidermis, dermis and hypodermis. Whether these changes are cause, effect or associated with is not settled. The most obvious driving force in the cycle appears to be the follicular papilla and the perifollicular mesenchyme. Important structural changes occur in the papilla during the hair cycle. The papilla is at the largest in full anagen and becomes smaller and more compact in telogen. The size of the papilla dictates the size of the follicle, and the size of the papilla itself is dictated by the body location. The variable papilla dimensions during the hair cycle are reflected in the changing extracellular matrix, with an accumulation of proteoglycans, such as versican, alkaline phosphatase positive cells, and accumulation of the protease inhibitor nexin-1 [8–10]. The vascular component also becomes more prominent during the growth phase, and the papilla expresses the vascular endothelial growth factor [11, 12].

Factors from the papillary mesenchymal cells act on the epithelium of the follicle. On the initiation of anagen, factors from the papilla influence stem cells of the hair follicle that are receptive to inductive signals. These cells reside in the bulge area [13], and they are also found in an apparently fewer number in the lower anagen follicle as well [14].

Co-ordination between successive hair cycles

In subjects with low hair density, most follicles contain only one hair, and some others may appear empty [15]. In subjects with high hair density, follicular orifices frequently contain several hairs. This may be because of the presence of more than one hair follicle sharing in common a single orifice. Delayed or conversely early teloptosis may also influence these patterns [7]. Teloptosis can occur concurrently as the hair follicle initiates the next early anagen stage or has been in anagen for some time. Indeed, the follicle often retains its club hair until the new hair emerges from the skin surface. However, in some physiological and pathological conditions, the hair is lost before the next hair is visible. During the latency period, the hair follicle appears empty at the clinical inspection [15–20]. The delay before the extrusion of the next generation of hair corresponds to the hair eclipse phenomenon. When present, this physiological feature may be more or less prolonged, reaching 4–7 months in average [17, 18]. It obviously influences the hair density of the scalp.

Theoretically, the hair eclipse may result from a too early teloptosis, delayed initiation of the anagen I stage or from a slowdown or blockage in any of the following anagen stages until anagen V ends. Thus, the underlying causative mechanisms are probably

diverse and remain yet undisclosed. Two typical examples of generalized hair eclipse phenomenon are given by the arrest of hair growth in the anagen IV stage during alopecia areata [11] and in the transient baldness occurring in some newborns or after chemotherapy. In our experience, the chronic telogen effluvium [21] may also be followed by the hair eclipse phenomenon. The diversity of causes and mechanisms implicated in the hair eclipse phenomenon is remarkable. Hence, this condition is not restricted to a specific hair cycle phase as suggested by the term kenogen [22].

It is often considered that the successive phases of the hair cycle follow a regular progression. However, the eclipse phenomenon is a clue suggesting that this assumption may not be valid. In addition, at a given time, the speed of growth of anagen VI hairs may be variable. In general, subjects with little or no baldness exhibit a clear difference between fast- and slow-growing hairs [23]. By contrast, a continuous distribution of hair growth rate has been reported in subjects with alopecia [23]. Temporary reduction in the speed of hair growth is likely to occur, either spontaneously or in response to physical or chemical stress. When the stress is severe enough, the hair shaft diameter decreases at the time of insult [24]. The hair cycle may also be severely altered with passage to a dystrophic anagen stage [1].

The anagen phase can be induced by injury to the hair follicle. This phenomenon represents a model to study the anagen I switch and the following processes of hair growth. Wounding the skin causes a local release of paracrine signals initiating anagen in a way similar to that for the spontaneous onset of anagen. The key factor may be injury to the skin surface or to the hair follicle. Indeed, hair plucking, vigorous shaving or chemical exposure to depilatory agents were considered to induce anagen [25], but cutting the hair without causing injury to the skin does not [26]. However, plucking experiments and mathematical modellings [27, 28] indicate that hair removal is not always followed by the reset of the follicle to telogen or by a continuation of the anagen VI stage. These considerations, including induction of teloptosis and the hair eclipse phenomenon, are for instance of importance when interpreting the success of laser hair removal [29, 30].

Microinflammation abutted on the permanent portion of the hair follicle may be one of the causes responsible for the hair eclipse phenomenon. Clinically imperceptible inflammation is present around hair follicles in androgenic alopecia and chronic telogen effluvium [1, 31–38]. Microinflammation is likely boosted by the presence of some microorganisms in the infundibulum [34, 37, 39]. It may interfere with the complex controls of the hair follicle cycling. Reducing the microinflammation by topical antifungals has been reported to improve the androgenic alopecia status [34, 37]. According to these findings, anti-inflammatory agents could be helpful to control some processes of hair shedding, and to reduce the duration of the hair eclipse phenomenon.

Synchronizers and the hair eclipse phenomenon

All chronobiological events are under the influence of endogenous pacemakers. Other periodical signals called synchronizers are used by the organism to modify the biological clock. In these respects, control of the hair follicle cycling occurs by means of cell-to-cell signalling, exhibiting a synchronizer function. In many cases, cell communication is ensured by messenger molecules that may be soluble or bound to cell surface. Relevant to the action of these molecules is that the signalling works through receptors, so that the control of a given process may involve the restricted expression of a given ligand or its receptor. In addition, the timing of ligand and receptor is a critical step. The instructive or permissive synchronizer signals may arise from epithelial or mesenchymal cells, and from adjacent cells or distant cells. Finally, a given signal may generate the morphological event or it may stimulate other signals that, in turn, initiate a highly complex, epithelial to epithelial, epithelial to mesenchymal, mesenchymal to epithelial or mesenchymal to mesenchymal interacting cascades.

The presence or the lack of a number of mediators can be involved in the eclipse phenomenon. The underlying biological mechanisms are likely unrelated and still different from those involved in the hair eclipse present during ageing, androgenic alopecia and a few other scalp conditions. Distinct biological factors and modes of signalling mediate the complex cellular interactions that exist in the hair. Soluble growth factors, peptide hormones and other cytokines such as interleukines are diffusable peptide molecules, secreted by selected cell types that exert biological activities or responses on the same cells, adjacent cells, and tissues or distant cells and tissues.

Growth factors in concert with other regulatory molecules appear to be the fundamental mediators of cellular communication and tissue organization within the hair. Some of them may be regarded as

chronobiologically active synchronizers. Peptide growth factors mediate signalling via specific cell surface receptors. In contrast, the more lipophilic, smaller sterol hormones easily transit the lipid-rich cell membrane and bind to its cognate intracellular receptors. An increasing number of membrane-associated adhesion molecules, including the integrins, are being found to be regulated in expression and activity by different growth factors and, in turn, contribute to the cell–cell and cell–matrix interactions within the hair. Cell adhesion molecules are also critically involved in the generation and transmission of biological signals that control proliferation and differentiation of various cell types of the hair.

Conclusion

The hair eclipse phenomenon is not one specific phase of the hair cycle. It results from very different causes. It influences hair density and thus has consequences in cosmetology. Defects in chronobiological synchronizers of the hair cycle should be involved in this process.

On a cosmetic point of view, the hair eclipse phenomenon should be shortened as much as possible on the scalp. By contrast, it should be extended when unwanted facial and body hair is an embarrassing and annoying problem.

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