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Exploring the "brain-skin connection": Leads and lessons from the hair follicle

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ABSTRACT

Research into how the central nervous system (CNS) and the skin of mammals are physiologically connected and how this "brain-skin connection" may be therapeutically targeted in clinical medicine has witnessed a renaissance. A key element in this development has been the discovery that mammalian skin and its appendages, namely human scalp hair follicles (HFs), not only are important, long-underestimated target tissues for classical neurohormones, neurotrophins and neuropeptides, but also are eminent peripheral tissue sources for the production and/or release of these neuromediators. This essay summarizes the many different levels of biology at which human scalp HFs respond to and generate a striking variety of neurohormones, and portrays HFs as prototypic, cyclically remodelled miniorgans that utilize these neurohormones to autoregulate their growth, hair shaft production, rhythmic organ transformation, pigmentation, mitochondrial energy metabolism, and immune status. The essay also explores how preclinical research on human scalp HFs can be exploited to unveil and explore "novel" and clinically as yet untapped, but most likely ancestral functions of neurohormones within mammalian epithelial biology that still impact substantially on human skin physiology. Arguably, systematic investigation of the "brain-skin connection" is one of the most intriguing current research frontiers in investigative dermatology, not the least since it has reversed the traditional CNS focus in studying the interactions between two key organ systems by placing the skin epithelium on center stage.

1. Introduction

Clinicians have long appreciated how intimately brain activities and skin functions are connected, for example in patients with chronic inflammatory and pruritic skin diseases ranging from atopic dermatitis over chronic urticaria and prurigo nodularis to psoriasis, and that psychoemotional stress can trigger or aggravate these dermatoses profoundly [1–5]. Moreover, the cutaneous signs and symptoms associated with a wide variety of neuroendocrine abnormalities, such as in acromegaly, hyperprolactinemia, Cushing's and Addison's disease as well as in malignancy-associated ectopic hormone production, amply illustrates the clinical importance of classical neurohormones for human skin function in health and disease. In fact, the pathological neurohormone serum levels seen in these patients typically are associated with abnormalities in hair growth and/or hair pigmentation [6].

Yet, mainstream neuroendocrinology research has shown little interest in the intriguing cutaneous phenomena associated with abnormal neurohormone serum levels. Therefore, the current essay re-explores the "brain-skin connection" from a neuroendocrine perspective. It does so by focusing on one of the defining features of mammals, the hair follicle (HF), since its neuroendocrinology [7] holds multiple lessons in store for anyone who wishes to understand how and why CNS activities and skin functions are intertwined so inexorably and how this specific aspect of the "brain-skin connection" [1,2] may be targeted therapeutically.

2. "Hairy" matters in the "brain-skin axis": psychoemotional stress and hair growth

Perhaps, the visually most striking clinical illustration of the importance of the "brain-skin connection" is a rare hair phenotype, which has long fascinated physicians, scientists, laymen, and poets alike: the phenomenon of "overnight greying". Most frequently, this has been reported to have occurred in individuals shortly after these had suffered a severe psychoemotional trauma and a corresponding systemic stress response.

In most documented cases, this phenomenon appears to reflect a fulminant episode of the relatively rare diffuse variant of a (typically focal) autoimmune hair loss disorder, alopecia areata, where only fully pigmented anagen HFs are attacked by a cytotoxic

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perifollicular inflammatory cell infiltrate, which leads to the shedding of pigmented hair shafts only [8]. This de-masks the unaffected, preexistent, yet previously visually unimpressive grey/white hairs, thus generating the illusion of "overnight greying". The fact that psychoemotional stressors have been documented to trigger episodes of hair loss attacks in a small minority of alopecia areata patients raises the possibility that the systemic neuroendocrine stress responses that go along with such stressors can elicit neurogenic skin inflammation that at least contributes to the triggering of alopecia areata [1,9].

However, extremely rarely, cases of this phenomenon have been photodocumented where alopecia areata cannot be invoked as a plausible explanation for "overnight greying", yet where a massive psychoemotional stress response has preceded a sudden switch-off of HF pigmentation, while hair shaft production as such continues, albeit with a post-stress change in hair shaft quality/diameter [10]. In both instances, the intriguing question arises on which cellular and molecular basis the major neuroendocrine and neuroimmunological changes associated with severe psychoemotional stress responses can elicit such a dramatic hair phenotype (for discussion see [9,10]). In this respect, studying the HF promises to provide us with a unique magnifying lense for studying translationally relevant aspects of the "brain-skin axis", namely the long-disputed impact of psychoemotional stress and hair growth.

3. Stress-induced perifollicular inflammation

Mouse models of perceived stress have indeed revealed that "stress" can very rapidly induce substantial perifollicular neurogenic inflammation, which subsequently inhibits hair growth profoundly. This body of work has identified at least three key players that collaborate to elicit this HF-targeting neurogenic skin inflammation: perifollicular mast cells, which are exquisitely sensitive to key neuroendocrine stress mediators such as corticotropin-releasing hormone (CRH), the key stress response-associated growth factor, i.e. nerve growth factor (NGF), and the prototypic stress-associated neuropeptide, substance P (SP), which is released from sensory nerve endings that innervate the HF unusually densely and whose synthesis in dorsal root ganglion neurons is NGF-dependent [1,11,12]. In addition, perceived stress activates perifollicular dermal dendritic cells in murine skin [13]. Moreover, high serum and intracutaneous levels of CRH, SP, NGF and degranulating perifollicular mast cells, by themselves, can exert strong, direct hair growth-inhibitory effects on actively growing (anagen) HFs in both mice and humans [14–17].

Over the past two decades, our understanding of the molecular and cellular basis of stress-induced neurogenic skin inflammation and itch (pruritus) has steadily increased and the underlying mechanisms have become much better understood. This includes the dissection of specific molecular pathways through which the classical stress mediators (CRH, cortisol, NGF, SP) and additional key stress-associated neurohormones, namely adrenocorticotropin (ACTH) and prolactin (PRL), as well as the neuropeptides calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) regulate skin inflammation, pruritus and impact on a wide range of inflammatory skin diseases [1,2,5]. Together, this has invigorated and refocused research into how the CNS and the skin of humans and other mammals are physiologically connected in a bidirectional manner via a large set of defined neuromediators [1,2,4,5,7,18].

As a consequence, it has become a recent focus of interest how this "brain-skin connection" may be therapeutically targeted in clinical medicine. Moreover, this has caused a genuine renaissance of skin neuroendocrinology as a distinct field of research [5,7,18,19]. More recently, research into the "brain-skin axis" has been enriched by the recognition that, besides its intimate connection with the endocrine and immune systems, this axis is itself embedded into a wider "brain-gut-skin axis", on which skin and gut microbiota impact profoundly [3,20] – a revival of long forgotten concepts that a much earlier generation of dermatologists had already contemplated in depth [20].

A momentous development in this context was the discovery that neurohormones, neuropeptides, and neurotransmitters are not only expressed and secreted by specialized neuroendocrine cells, e.g. in the hypothalamus, pituitary or adrenal gland, and/or secreted by sensory cutaneous nerve fibers, but are also synthesized by resident cells in mammalian skin itself – notably including human skin epithelium, i.e. human epidermal and HF keratinocytes as well as sebocytes, which are derived from HF epithelium during skin development [21]. From a humble start in the second half of the last century, for example through research on the neuroendocrine controls of animal fur coat cycling and pigmentation, the detection of alpha-melanocyte stimulatory hormone (αMSH) in mammalian skin and the discovery of pilosebaceous units as hair cycle-dependent sources of proopiomelanocortin (POMC) transcription and melanocortin and ß-endorphin production, cutaneous neuroendocrinology has now firmly established itself as a fast-moving and translationally very relevant field in skin research [1,2,5,6,18,19]. Arguably, this now represents one of the most exciting and fertile research frontiers in contemporary investigative dermatology. Moreover, skin neuroendocrinology has reversed the traditional focus on the CNS and specialized neuroendocrine glands when studying the "brain-skin connection" by placing the skin epithelium on center stage, instead [6,18] (see below, "Evolutionary considerations").

4. Neurohormone-sensitive and – producing human scalp hair follicles as discovery tools for translational research into the "brain-skin connection"

In this development, hair research has played a central role and continues to do so, namely the discovery that human scalp HFs, not only are long-underestimated target tissues for classical neurohormones and neuropeptides, but also are eminent peripheral tissue sources for the production and/or release of these neuromediators (Table 1). As shown in this table, human scalp HFs respond to a striking variety of neurohormones, and represent prototypic, cyclically remodeled miniorgans [22] that express an astounding variety of neurohormones which autoregulate their growth, hair shaft production, cyclic organ transformation, pigmentation, mitochondrial energy metabolism, and immune status. We owe most of the findings and concepts in this field to preclinical research with microdissected, organ-cultured human scalp HFs. This highly instructive assay system pioneered by Michael Philpott et al. [23] and greatly extended by others [24], can be exploited to unveil "novel" and as yet largely untapped functions of classical neurohormones within epithelial biology that still impact substantially on human skin physiology.

4.1. Hair biology: essentials

Before this is illustrated with a few examples (see below), some central concepts of HF biology must be called to mind. HFs exert many more, but often forgotten, functions than the production of pigmented hair shafts – an evolutionary feat that, by itself, already expanded the functional properties of mammalian skin substantially and bestowed it with distinctive selection advantages over competing species, e.g. by providing a dense coat of highly efficient, skin-protective, sensory and thermoinsulating epithelial fibers; these also operate as a widely visible instrument of psychosocial and reproductive communication, as a wick for dispersing sebum and pheromones, and as a habitat for a rich resident microflora [20,22].

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