

Commentary

Stress and the Hair Follicle: Exploring the Connections

Vladimir A. Botchkarev

From the Department of Dermatology, Boston University School of Medicine, Boston, Massachusetts

All living organisms are constantly challenged by a diversity of exogenous (environmental, psychological, social) and endogenous stimuli or stressors, which induce general or local biological responses to protect or adapt the organism to the stressor(s).¹ The systemic biological response of the organism to exogenous stressors (or classical stress response) includes activation of the hypothalamic-pituitary-adrenal axis and release of hypothalamic corticotropin-releasing hormone (CRH) that activates pituitary CRH receptors (CRH-R) followed by the production and release of proopiomelanocortin-derived peptides and adrenal hormones.^{2,3} Systemic stress response also includes the modulation of the autonomic nervous and immune systems: neuroendocrine hormones and neurotransmitters influence the function of the immune system that reciprocally regulate CNS functions through cytokine release.⁴

Skin as a Target for Systemic and Local Stress Responses

Skin is an organ that covers and protects body from environmental (physical, chemical, or biological) stressors, which include temperature, ultraviolet radiation, mechanical trauma, biological insults, and chemicals. Skin is richly innervated by sensory nerves^{5,6} that transmit information about the effects caused by environmental stressors to the central nervous system to develop the systemic response of the organism appropriate to its external environment. In turn, the hormones secreted during the systemic stress response and neurotransmitters of the autonomic nerve fibers innervating skin may target skin cells and modulate or affect their functions, depending on circumstances.⁷

Data obtained during the last decade suggest that the major molecular components that mediate the systemic response to environmental stressors (CRH and proopiomelanocortin peptides), as well as neurotransmitters and cytokines are also expressed in the skin.⁷⁻¹⁰ Specifically,

it is shown that epidermal keratinocytes, fibroblasts, mast cells, and immune cells express CRH-R1, whereas CRH protein is expressed in keratinocytes and dermal nerve fibers.^{11,12} The proopiomelanocortin peptides (ACTH, α -MSH, β -endorphin) have also been detected in keratinocytes, melanocytes, and Langerhans cells.¹³⁻¹⁷ Neurohormones, cytokines, and neurotransmitters secreted by the major structural components of the skin (keratinocytes, melanocytes, fibroblasts, immune and endothelial cells, nerve fibers) form a molecular network of signals that is activated during cutaneous response to different environmental stimuli.¹⁰ Therefore, together with the systemic stress response, environmental stressors may also induce the stress response inside of the skin, which may operate as a local equivalent of the hypothalamic-pituitary-adrenal axis.¹⁰

Numerous indications suggest that both systemic and local responses to stressors may have roles in the onset or exacerbation of a variety of skin diseases.¹⁸ Psychological stress is now considered as an important etiological factor in the onset of psoriasis, atopic dermatitis, pruritus, and urticaria.¹⁸ Sensory neuropeptides and neurotransmitters released by sensory and autonomic nerve fibers that innervate the skin can directly modulate functions of keratinocytes, melanocytes, Langerhans cells, mast cells, endothelial cells, and immune cells.^{15,19-21} Among the molecules substance P, calcitonin gene-related peptide, vasoactive intestinal peptide, somatostatin, noradrenaline, and acetylcholine have been reported to effectively modulate skin and immune cell functions such as cell proliferation, cytokine production, or antigen presentation under normal and pathological conditions.^{15,19-22} This further proves the concept that skin serves as an important target for systemic and local stress responses.

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Address reprint requests to Vladimir A. Botchkarev, M.D., Ph.D., Department of Dermatology, Boston University School of Medicine, 609 Albany St., Boston, MA 02118. E-mail: vladbotc@bu.edu.

Neurohormones, Neuropeptides, and Neurotransmitters—Are They Capable of Influencing Hair Growth?

Hair follicle is a skin appendage that shows cyclic activity in postnatal life with periods of active growth and hair formation (anagen), rapid apoptosis-driven involution (catagen), and relative resting (telogen).^{23–25} Hair follicle transition between distinct hair cycle stages is governed by epithelial-mesenchymal interactions between the follicular keratinocytes and dermal papilla fibroblasts.^{24–26} Growth factors forming a molecular network of signals that the epithelium and the mesenchyme send to each other during the hair cycle belong to the Wnt, transforming growth factor- β /bone morphogenetic protein (BMP), Hedgehog, fibroblast growth factor, Notch, epidermal growth factor, tumor necrosis factor, and neurotrophin families.^{24–26}

Accumulating evidence of the data suggests that neurohormones, neurotransmitters, and cytokines released during the stress response may also significantly influence the hair cycle.^{13,27} Actively growing hair follicles in mice and humans show expression of CRH-R1 and melanocortin-1 receptor (MC-1R) in the follicular epithelium and mesenchyme.^{11,13,14} Administration of ACTH into murine telogen skin causes mast cell degranulation and activation of hair growth in resting hair follicles.²⁸ However, ACTH treatment also induces premature hair follicle anagen-catagen transition.²⁹ Similarly to the stress-induced thymic involution, glucocorticoids stimulate apoptosis in the follicular epithelium leading to premature hair follicle involution.³⁰ Thus, the effects of neurohormones on hair follicle growth seem to be more complex than previously appreciated and strongly depend of hair cycle stage.

The hair follicle is richly innervated by sensory and autonomic nerve fibers. In murine dorsal skin, nerve fibers that innervate hair follicles form two networks: around the distal outer root sheath in the subepidermal dermis (follicular network A) and around the outer root sheath between the sebaceous gland and the insertion point of the arrector pili muscle (follicular network B).^{31–33} The follicular network A consists of unmyelinated C-fibers expressing such neuropeptides as substance P, calcitonin gene-related peptide, peptide-histidine-methionin (PHM), and the enzymes choline acetyltransferase and tyrosine hydroxylase.^{32,33} Follicular network B consists of a collar of longitudinal and circular nerve fibers arranged in the manner of a palisade around the outer root sheath of the hair follicle. These nerve fibers function as slowly adapting mechanoreceptors and show expression of calcitonin gene-related peptide and choline acetyltransferase.^{5,32,33} Together they fill the space between the sebaceous gland and the hair follicle epithelium adjacent to the bulge region and distal to the arrector pili muscle. In human hair follicles, substance P-positive nerves are also found in the dermal papilla.³⁴

The hair follicle bulge region contains a population of putative hair follicle stem cells.^{35–37} A close localization of sensory and autonomic nerve fibers and hair follicle

bulge raises a possibility that neuropeptides and neurotransmitters may influence stem cells or their progeny and modulate hair cycle.²⁷ Indeed, bulge keratinocytes show expression of β 2-adrenoreceptors and neurokinin-1 receptor³² (Botchkarev et al, unpublished observations). Treatment of telogen mice by substance P or by norepinephrine-depleting agents lead to stimulation of hair growth, whereas substance P administration into anagen skin results in premature catagen development.^{29,38} Recent data suggest that denervation of murine skin leads to down-regulation of expression of hair keratin genes.³⁹ Taken together, these data suggest that neurohormones, neuropeptides, and neurotransmitters may significantly influence cyclic activity of the hair follicle further supporting the hypothesis that hair follicles represent an important target for stressors.

Toward Understanding the Molecular Mechanisms of the Hair Follicle Response to Stressors

There are several indications in the literature suggesting that severe psycho-emotional stress may cause the onset of alopecia areata.^{40–42} Also, it has been long debated whether or not environmental or psychosocial stressors can significantly influence hair growth.^{13,43–46} First systematic studies to address this intriguing question have been recently performed by Hair Research Laboratory of R. Paus (University of Hamburg, Hamburg, Germany) and a neuroimmunological group with strong focus on stress-triggered dysbalances of physiological homeostasis led by P. Arck (Humboldt University, Berlin, Germany).⁴⁷ Investigators showed that in mice audiogenic (sonic) stressor induces appearance of apoptotic cells in resting hair follicles and inhibits keratinocyte proliferation.⁴⁷ Furthermore, sonic stressor causes significant changes in skin immune system: increase of number of activated perifollicular macrophage cluster and mast cell degranulation, as well as down-regulation of intraepithelial $\gamma\delta$ T cells.⁴⁷ Interestingly, these changes could be abrogated by administration of selective substance P receptor antagonist suggesting involvement of substance P in realization of hair follicle response to stressor.⁴⁷

In the article published in the current issue of *The American Journal of Pathology*, Arck and colleagues⁴⁸ follow-up their previous work and provide further evidence for existence of “brain-hair follicle axis.” They show that audiogenic stress also induces significant changes in actively growing hair follicles and promotes their transition into the involution phase. Premature termination of hair follicle growth induced by stressor is associated with up-regulation of keratinocyte apoptosis, increased mast cell degranulation, and appearance of perifollicular inflammatory infiltrates of activated macrophages.⁴⁸ Furthermore, the authors show that most of these hair growth-inhibitory effects of stressor can be reproduced in nonaffected mice by administration of substance P, whereas substance P receptor antagonist reduces the stress-induced hair growth inhibition.

Interestingly, Arck and colleagues⁴⁸ describe the increase of close contacts between substance P-containing nerve fibers and mast cells in skin after stressor exposure. Mast cell-nerve associations in skin have been noticed previously during the normal hair cycle⁴⁹ and also in a variety of pathological situations including wound healing, atopic dermatitis, and psoriasis.^{6,50} Substance P is a potent mast cell secretagogue and may stimulate the release of proinflammatory cytokines such as tumor necrosis factor- α by mast cells.^{19,22} Importantly, CRH released during the stress response is also capable of inducing mast cell degranulation.^{51,52} These data suggest that mast cells are important local modulators of the hair follicle response to stress exposure and raise a possibility to speculate that inhibitors of mast cell secretory activity may also be effective to prevent stress-induced hair growth alterations.

The exciting data presented by Arck and colleagues⁴⁸ also raises several intriguing questions about the mechanisms involved in the hair follicle response induced by audiogenic stressor. It seems interesting to define whether substance P plays a major role in mediating the effects of audiogenic stress on the hair follicle, or other components of the systemic and local stress response (CRH, proopiomelanocortin peptides, glucocorticoid hormones, autonomic neurotransmitters) are also involved in stress-associated hair growth inhibition. Also, the cellular targets for substance P in the hair follicle during the stress response remain to be determined. In addition, it seems to be logical to ask which apoptotic pathways are activated in hair follicle keratinocytes after stress exposure and whether or not audiogenic stress also stimulates apoptosis in hair follicle melanocytes. Most importantly, data presented by Arck and colleagues⁴⁸ provides a model of depilation-induced hair cycle as a tool for researchers to further investigate the molecular mechanisms of hair follicle response to stress exposure. Hopefully, use of this model would bring important new knowledge into our understanding of stress-induced hair loss and would help to design in the near future new approaches for the treatment of stress-associated hair growth disturbances.

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