

Neuroimmunoendocrine circuitry of the 'brain-skin connection'

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The skin offers an ideally suited, clinically relevant model for studying the crossroads between peripheral and systemic responses to stress. A 'brain-skin connection' with local neuroimmunoendocrine circuitry underlies the pathogenesis of allergic and inflammatory skin diseases, triggered or aggravated by stress. In stressed mice, corticotropin-releasing hormone, nerve growth factor, neurotensin, substance P and mast cells are recruited hierarchically to induce neurogenic skin inflammation, which inhibits hair growth. The hair follicle is both a target and a source for immunomodulatory stress mediators, and has an equivalent of the hypothalamus-pituitary-adrenal axis. Thus, the skin and its appendages enable the study of complex neuroimmunoendocrine responses that peripheral tissues launch upon stress exposure, as a basis for identifying new targets for therapeutic stress intervention.

Principles of neuroimmunological and neuroendocrine responses to psychological stress

A central paradigm in stress research is that the endocrine, immune and nervous 'super-systems' engage in multiple interactions during the response of the body to acute and chronic stress. Each system is also individually vulnerable and responds to defined stressors [1] (Figure 1). This network shares respective ligands and/or their cognate receptors [2]. Whether or not a healthy balance of protective or damaging effects of stress responses is achieved is influenced by the newly developed stress concept of allostasis [3]. In this concept, allostasis is defined as the adaptation of the nervous, endocrine and immune systems to maintain stability through change (triggered, for example, by unpredictable events, such as conflict in social hierarchies and competition for resources, or predictable events, such as seasonal changes). An inefficiently managed adaptation is referred to as allostatic overload [3].

In response to stress, neurohormones, neurotransmitters, neuropeptides and neurotrophins stimulate a series of adaptation responses (Figure 1 and Table 1). These typically include behavioral, cardiovascular, metabolic, endocrine and immunological changes [4–12];

the immunological changes range from immunosuppression to inflammation [6,12,13] (Figure 1 and Table 1). These divergent and, at times, seemingly contradictory effects reflect the dual and multifunctional role of the immune system as both a sensory and an effector organ in the stress response.

The immune system also regulates the central nervous system (CNS). Cytokines and other inflammatory mediators can signal the brain, thus, influencing behavior and other complex body reactions (Figure 2). For example, mast-cell histamine increases the expression of corticotropin-releasing hormone (CRH) mRNA in the hypothalamus, which activates the hypothalamic pituitary-adrenal (HPA) axis [14]. Moreover, CRH secretion could be triggered by IL-6 and IL-1 [15], both of which are also released from mast cells; conversely, CRH stimulates IL-6 release [16]. Proinflammatory cytokines (e.g. via activation of innate immunity in response to infections) can induce sickness behavior and depressive symptoms and might aggravate stress perception [17].

Several diseases have long been recognized to be triggered or aggravated by psychological stress, such as inflammatory bowel disease [18], migraines [19], experimental allergic encephalomyelitis [20] and multiple sclerosis [21]. Also, stress perception during pregnancy can trigger pregnancy complications [22,23].

A growing list of stress mediators has been defined in recent years (Table 1). However, their relative functional importance, hierarchy and interactions during central and peripheral responses to stress are largely unclear. As the most upstream element of the central HPA axis and as a prototypic 'stress hormone' that is also generated by several peripheral cells, CRH has a key role in coordinating and controlling complex responses to psychological stress, both systemically and locally [24]. In fact, it has been proposed that CRH be renamed stress-response hormone (SRH) to reflect its expanding role [5].

CRH and its receptor (CRHR) are expressed at the gene and protein level in the skin [25,26], whereas CRH-like immunoreactivity is present in the dorsal horn of the spinal cord and dorsal root ganglia [27]. In addition to the often-quoted immunosuppressive effects of CRH, relevant examples of pro-inflammatory actions of CRH have been

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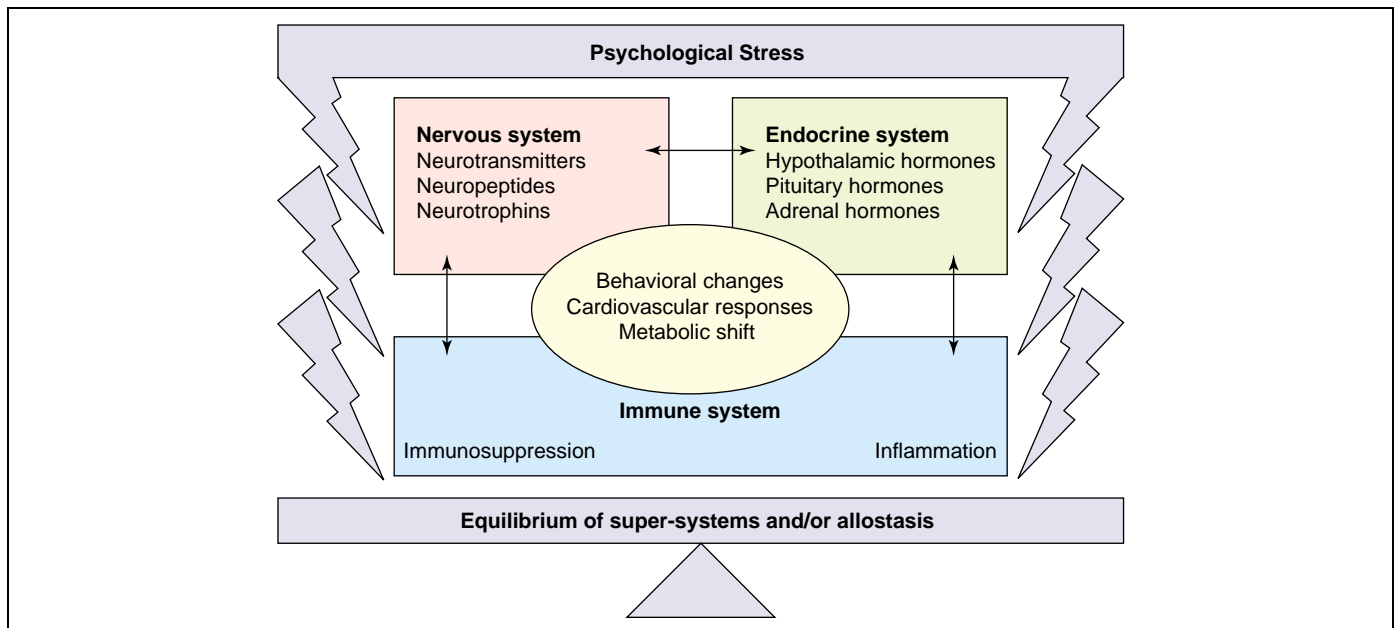


Figure 1. Principles of the stress response. The coordinated activation and eventual downregulation of the three super-systems (the nervous, endocrine and immune systems) ensures equilibrated stress-response patterns that result in allostasis. Allostatic overload causes disequilibrium, upregulation of immune responses and disease.

introduced [28] and include carrageenin-induced aseptic inflammation [29] and arthritis, where both CRH and urocortin (Ucn) have been identified in the joints [30]. In fact, mast cells in the joints of patients express CRHR [30]. Moreover, inflammatory arthritis, which is absent in W/W^u mast cell-deficient mice, is greatly attenuated in CRH-deficient mice [31] and is blocked by the CRHR-1 antagonist antalarmin [32].

Skin: the ultimate model for neuroimmunological stress research

In the skin, 'itch' (pruritus), excessive sweating (hyperhidrosis) and 'flushing' (facial erythema), and many dermatoses such as atopic dermatitis, psoriasis, seborrhoeic eczema, prurigo nodularis, lichen planus, chronic urticaria and alopecia areata, can be triggered or aggravated by stress [33].

Table 1. Key protagonists in the response to psychological stress

Stress mediator	Main biological effect	References
Hormones of the HPA axis (CRH, ACTH, glucocorticoids)	Activate mast cells Upregulate production of IL-4, IL-6, IL-10, and IL-13 Inhibit the production of IL-12, IFN- γ , and TNF- α by antigen-presenting cells (APCs) and T helper (Th)1 cells	[29,45,60] [5,16,24,31] [13,24]
Prolactin (PRL)	Participates in early and late T-cell activating events; contributes to a pro-inflammatory and apoptosis-prone environment	
Catecholamines	Regulate the immune system at regional, local and systemic levels via adrenergic receptors expressed on immune cells Induce lymphocytosis, affect lymphocyte traffic, circulation, and proliferation, and modulates cytokine production	[12]
SP	Stimulates or augments mast-cell activation Induces inflammation Induces lymphocyte proliferation Activates mast cells	[7,8,69] [7] [7,53]
PACAP	Activates mast cells, induces vascular permeability	[9]
Hemokinin	Activates mast cells, induces vascular permeability	[10]
NT	Activates mast cells, induces vascular permeability	[11]
CGRP	Inhibits proliferation and IL-2 release of T lymphocytes under immune challenges Activates mast cells, induces vascular permeability	
Neuropeptide Y (NPY)	Activates mast cells Induces adherence, chemotaxis, phagocytosis, lymphoproliferation, antibody and cytokine production	
β -endorphin	Activates mast cells, induces vascular permeability Effects chemotaxis and phagocytosis in macrophages Interacts with mast cells	
VEGF	Induces vascular permeability and angiogenesis	[55,56]
NGF	Promotes 'cross-talk' between neuronal and immune cells Acts as autocrine and paracrine factor in the development and regulation of immune cells Promotes monocyte and macrophage migration through vascular endothelium	[36]
SCF	Activates mast cells Promotes mast-cell proliferation and migration; activates mast cells	[48] [50]

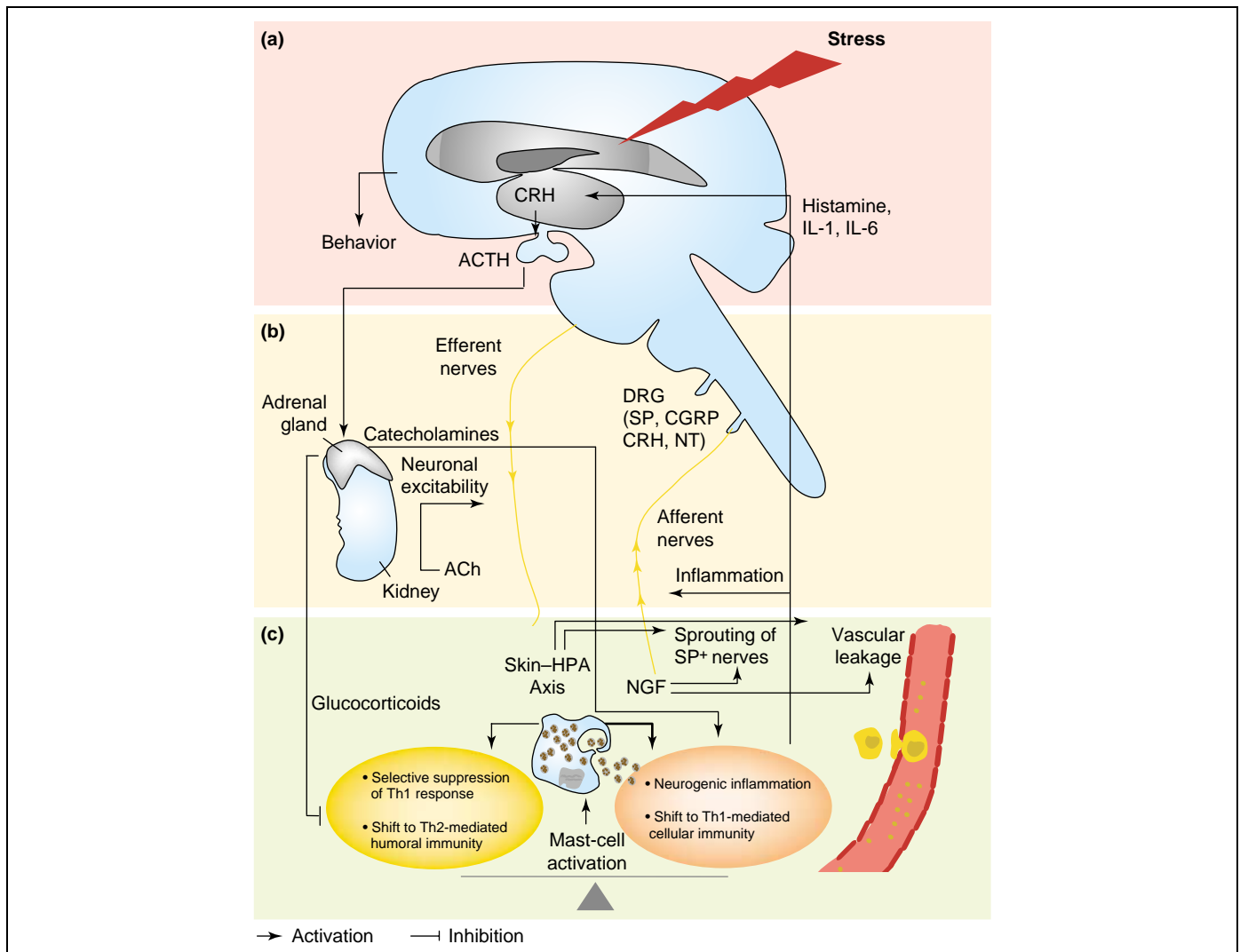


Figure 2. Communication routes between brain and skin immune system. (a) Stress perception results in the release of central stress-response coordinators, which in turn activate (b) the structural peripheral stress-response elements targeting the skin (c). The coordinated activation and eventual downregulation of the three super-systems (the nervous, endocrine and immune systems) ensures equilibrated stress-response patterns that result in allostasis. Allostatic overload causes disequilibrium, upregulation of immune responses and disease.

Psoriasis is the classic model of an inflammatory, hyperproliferative skin disease with an immune pathogenesis that is triggered or aggravated by psychological stress [34]. It was originally speculated that substance P (SP) [7], which is released in response to stress by sensory skin nerves, is the main stress mediator in psoriasis [35]. Nerve growth factor (NGF) has since been shown to control the intracutaneous release of proinflammatory neuropeptides, mast-cell degranulation and T-cell activation upstream of SP [36]. Interactions between mast cells, nerves and neuropeptides have also been implicated in atopic dermatitis [37]. Unlike psoriasis, atopic dermatitis is typically associated with elevated skin production of Th2 cytokines [38]. Recent work from a mouse model of sound-induced stress supports an NGF–SP–mast cell hierarchy in neurogenic skin inflammation [7,39]. The skin presents the largest interface with the environment. Moreover, the common neuroectodermal origin of the skin with the CNS is reflected throughout later life in its function as a crucial sensory organ, its unusually dense and intricate innervation and its role as

both a major target and source for most of the key players of neuroimmunoendocrine signaling, including numerous neurotransmitters, neuropeptides, neurotrophins and neurohormones that are generally associated primarily with the nervous and neuroendocrine systems (Table 1) [33,35,40]. Furthermore, the response patterns of the skin are easily discerned by the naked eye and tissue sampling for in-depth analysis is simple.

Skin mast cells as ‘central switchboards’ of stress response

Skin mast cells have a key role in the peripheral response to stress, acting as ‘central switchboards of neurogenic inflammation’ [41] and as major stress sentinels at the interface of the neuroimmunoendocrine environment [42].

Mast cells derive from a bone marrow progenitor and differentially mature in peripheral tissues, depending on local microenvironmental conditions. Mast cells are located perivascularly close to SP and calcitonin-gene related peptide (CGRP)-containing neurons [7]. Based on their prominent, preferential localization around nerves

and blood vessels, mast cells are now recognized as crucial first-line defense components of innate immunity, modulators of adaptive immune responses [43]. As 'tunable' effector and immunoregulatory cells [44], mast cells are thus ideally equipped and strategically placed to integrate and relay signals from all three super-systems during the peripheral tissue response to psychological stress.

Skin mast-cell activation, growth and/or survival are regulated by prototypic stress mediators: CRH, adrenocorticotropic (ACTH), SP, NGF and stem-cell factor (SCF) promote proliferation and activation, whereas catecholamines and corticosteroids inhibit mast-cell function [45]. For example, skin mast cells degranulate in response to acute stress or administration of CRH *in vivo* and *in vitro* [46], CRH administration induces neurogenic inflammation in rat skin, and CRH-neutralizing antibodies abrogate stress-induced degranulation of skin mast cells. NGF is released during stress [39,47] and promotes mast-cell maturation, survival, proliferation and degranulation [48]. Furthermore, stress-induced upregulation of SP results in activation/degranulation of skin mast cells [7] via the high affinity SP receptor neurokinin-1 (NK-1) [49], which is upregulated by IL-4 or SCF [50].

In addition to IgE and antigen [51], free immunoglobulin light chains [52], anaphylatoxins, cytokines, hormones, endovanilloids and neuropeptides can all

trigger mast-cell secretion [53]. The neuropeptides triggering mast-cell secretion include SP [7], neurotensin (NT) [11] NGF [54] and hemokinin A [10], as well as pituitary adenylate cyclase activating polypeptide (PACAP), which is localized in dermal nerve fibers [9] (Figure 3). Mast cells secrete a multitude of vasodilatory and proinflammatory mediators, such as histamine, heparin, kinins, proteases (preformed) and leukotrienes, prostaglandins, nitric oxide (NO) and cytokines (newly synthesized). In addition to histamine, vasoactive intestinal polypeptide (VIP) and tumor necrosis factor- α (TNF- α), mast cells also release vascular endothelial growth factor (VEGF) an isoform of which is particularly vasodilatory [55] (Figure 3). Moreover, overexpression of VEGF in mouse skin causes a psoriasiform skin inflammation [56], and mast cells might be involved in promoting the cascade of intracutaneous events that leads to psoriasis [36].

Mast cells can undergo ultrastructural alterations of their electron-dense granular core that are indicative of secretion but without degranulation, a process termed 'intragranular activation' [57]. Such activation might be associated with the ability of mast cells to release key mediators of skin inflammation selectively, for example, as reported for serotonin [58] or IL-6 and TNF [43]. IL-1 can stimulate selective release of IL-6 [59], whereas CRH

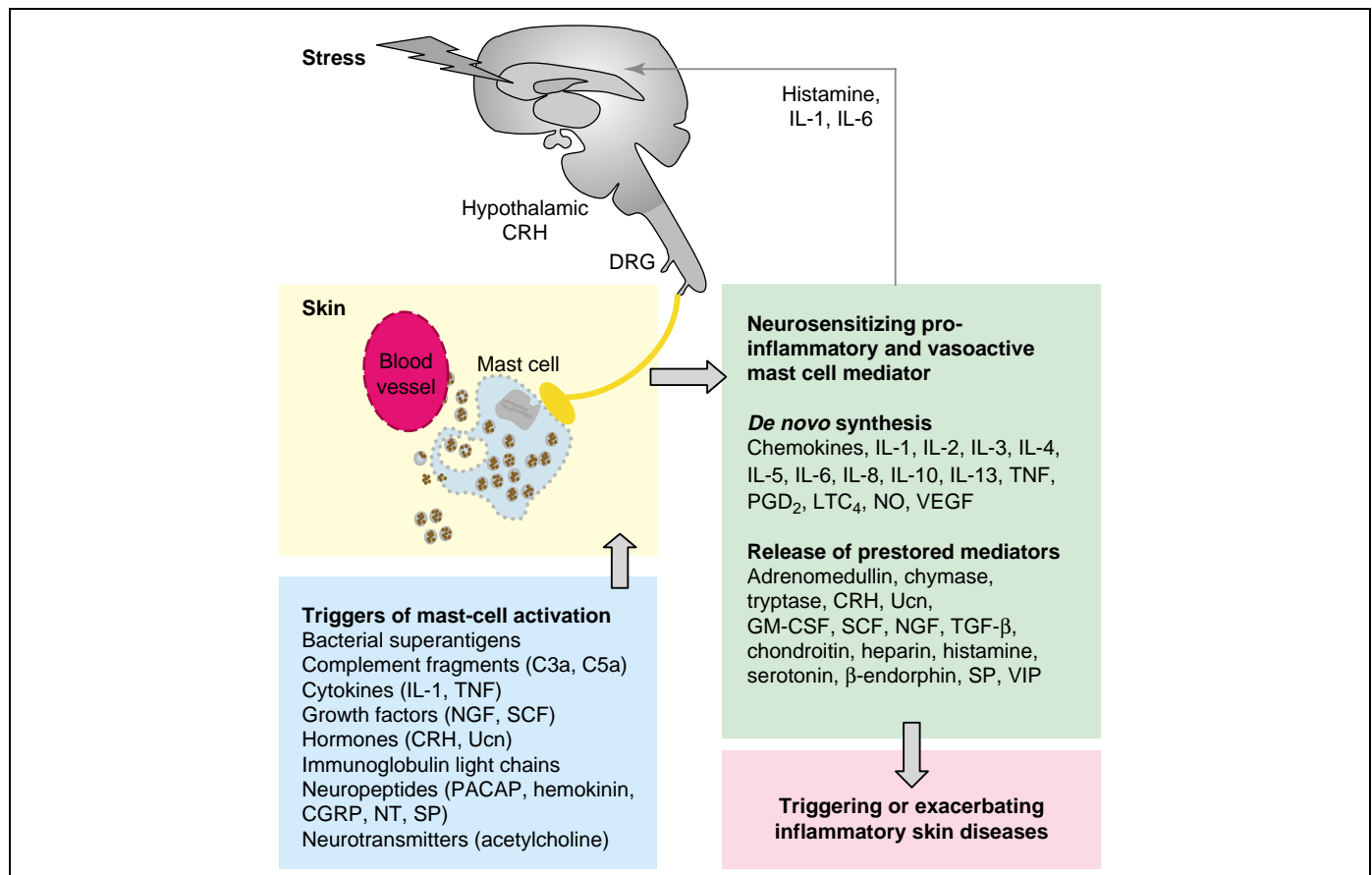


Figure 3. The stress-CRH-neuropeptide-mast cell connection in the pathogenesis of stress-induced skin diseases. Emotional, physical or oxidative stress could trigger CRH secretion, which activates CRH receptors in the skin leading to release of NK-1 agonists (neurokinin B or hemokinin) or NT. These could then trigger mast-cell activation, either directly or synergistically together with CRH, Ucn or other neuropeptides, such as NT or PACAP. Mast-cell-derived vasoactive, pro-inflammatory and neurosensitizing mediators, (such as IL-6, IL-8 and VEGF) then increase vascular permeability and contribute to the pathogenesis of inflammatory skin disorders. Points of possible prophylactic intervention include CRHR antagonists, which could block CRH action.

stimulates selective release of VEGF from mast cells [60]. Mast-cell-derived TNF enhances T-cell activation [43] and mast-cell-derived proteases activate proteinase-activated receptors (PARs) [61] on sensory neurons, which in turn augment the inflammatory response via the release of additional SP [33]. Tryptase-releasing mast cells are found in close proximity to PAR-2-expressing cells, such as keratinocytes, dermal endothelial cells and C-fibers during inflammation [33,61]; therefore, positive feedback loops centering on the mast cell can be envisioned by which stress-induced and/or neurogenic inflammation is rapidly upregulated (Figures 2 and 3).

It remains to be shown how this mast cell-driven inflammatory response to stress is attenuated and controlled, to avoid its perpetuation because it is characteristically seen during chronic inflammatory skin diseases, such as atopic dermatitis and psoriasis vulgaris [34,37]. The short half-life of some mast-cell products (owing to rapid cleavage), and the CRH-induced upregulation of immunosuppressive substances such as α -MSH [25,62], are important natural inhibitors of stress-induced inflammation.

Clearly, additional cell populations besides mast cells, particularly members of the innate immune system, such as natural killer (NK) cells or dendritic cells, are present in the skin and are likely to have a role within the brain–skin cross-talk.

Why the hair follicle is an ideal model for stress research

The multi-directional nature and the ever-increasing complexity of neuroimmunoendocrine communication during stress responses (Figures 1–3 and Table 1) requires that simplified but physiologically and clinically relevant research models are used to dissect how psychological stress regulates peripheral tissue functions.

The hair follicle represents a prototypic neuroectodermal–mesodermal tissue interaction system and is one of the most densely and intricately innervated of all peripheral tissues [63]. Production of a pigmented hair shaft and the cyclic transformation of hair follicles from their ‘resting’ state (telogen) into the active, hair-shaft-producing state (anagen) via apoptosis-driven organ involution (catagen) back to telogen (the ‘hair follicle cycle’) depends on coordinated tissue interactions: neuroectodermally derived cell populations (hair follicle keratinocytes and melanocytes) interact with a specialized mesenchyme (fibroblasts of the dermal papilla and the connective tissue sheath of the hair follicle), which retains striking inductive properties throughout adult life [64].

During the cyclic remodeling of the hair follicle, the perifollicular innervation shows substantial neural plasticity even in adult mammals [64,65], along with significant changes in both sensory and adrenergic skin innervation [66] and in mast cell–nerve contacts [7]. Much of this hair cycle-associated neural plasticity appears to result from the fact that the (continuously remodeled) hair follicle epithelium is a major intracutaneous source of neurotrophins, which are also used to control hair follicle development and cycling [39]. Moreover, the hair follicle connective tissue sheath is a major source of skin mast-cell progenitors and multipotent skin stem cells [7,39,67]. Given

the central role of mast cells in neurogenic inflammation and peripheral tissue stress responses, it is also interesting to note that perifollicular mast cells operate as important, although non-essential, modulators of hair follicle cycling [7,67]. Furthermore, murine hair growth *in vivo* and in skin organ culture is modulated by endogenous mast-cell secretagogues (such as SP, CRH and ACTH) that also act as major stress-response mediators [24,40,64].

The hair follicle is one of the most hormone-sensitive tissues known in mammalian biology. This includes a high degree of sensitivity to key ‘stress-associated’ hormones, such as CRH, ACTH, cortisol, catecholamines and prolactin, all of which act as hair growth modulators in human and/or mice via stimulation of high affinity receptors [26,40]. Surprisingly, the hair follicle is not only a prominent target but also operates as a potent peripheral source for all these ‘stress mediators’, including a fully functional peripheral equivalent of the HPA axis [40,64].

In addition to sensory skin nerves and skin mast cells, hair follicle keratinocytes prominently express functional vanilloid receptors (VR) and respond to VR1-stimulation, for example, by premature entry into hair follicle regression (catagen) [67]. It is, therefore, conceivable that endogenous VR1 ligands and activators (e.g. endovanilloids, such as anandamide, low pH, heat and select eicosanoids) also affect hair growth and perifollicular neurogenic inflammation under conditions of stress, both indirectly (e.g. via mast-cell activation) and directly (via effects on the hair follicle epithelium). Finally, ‘stress’ has long been implicated as a possible cause of hair loss, with stress recognized as a major aggravating factor, once hair loss has occurred [7]; stress-induced alopecia areata can also be associated with increased expression of CRHR-2 in the affected skin [68].

The hair follicle is therefore ideally suited to explore the inter-system communication that characterizes stress responses – including the ‘switchboard’ role of mast cells and peripheral tissue reactions to systemic stress-response networks. This notion becomes even more convincing if one considers that no other organ of the mammalian body is as easily accessible, available in such abundance and can be microdissected, organ cultured and experimentally manipulated with such relative ease as the skin.

Stress-induced hair growth inhibition in mice: leads and lessons

An established mouse model for chronic (sound-induced) psychological stress severely impairs mechanisms of immune tolerance [e.g. induces a Th1>Th2 cytokine ratio and decreases the expression of indoleamine 2,3-dioxygenase (IDO) and the presence of CD4⁺CD25^{bright} regulatory T (Treg) cells] [22]. Furthermore, increased expression of leukocyte function-associated antigen (LFA)-1 acts as a key peripheral blood marker for stress perception [22]. This stress model is now widely used in multiple approaches of neuroimmunological stress research, for example, to evaluate the effects of stress on bronchial hyperreactivity [69] or in experimental colitis [18].

In this model, it was recently substantiated that stress can exert profound inhibitory effects on hair growth,

accompanied by severe skin inflammation [7,39,70,71]. Exposure to sonic stress inhibited the growth of hair shaft-producing (anagen) follicles by premature induction of hair follicle regression (catagen) and by upregulating intrafollicular keratinocyte apoptosis [7]. In a distinct, complementary rodent stress model, mice exposed to foot shock showed a significantly retarded spontaneous switch of telogen follicles into anagen [72].

Sound stress exposure induces neurogenic inflammation characterized by increased NGF expression in the skin, perifollicular mast-cell degranulation and perifollicular accumulation of activated macrophages [7,39]. In the absence of functional mast cells or neurokinin-1 receptors (NK-1R) [71], and in the presence of NK-1R blockers [7,70] or NGF-neutralizing antibodies [39], stress exposure fails to induce premature hair follicle regression, neurogenic skin inflammation and hair follicle keratinocyte apoptosis [7,39,70,71]. Sound stress exposure is associated with an upregulation in the number of intracutaneous SP⁺ nerve fibers and of SP immunoreactivity in dorsal root ganglia (DRG), as measured by retrograde tracing [39]. Intriguingly, the hair growth inhibitory and proinflammatory effects of sonic stress can largely be mimicked by systemic administration of SP and NGF, and can almost be abolished by co-administering appropriate antagonists or neutralizing antibodies [7,39]. Therefore, in this model, psychological stress activates a defined, hierarchically organized cascade of events in which NGF, SP and mast cells apparently have the key roles (Figure 4).

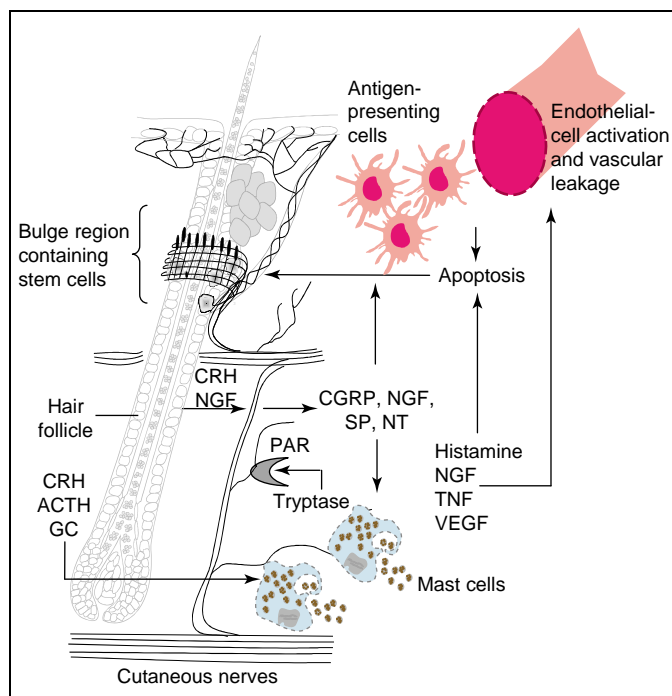


Figure 4. Mast cells: proximal mediators within the hierarchical stress-response network in skin inflammation. Upon stress exposure, CRH and NGF are increasingly present in the skin, either in the hair follicle, or secreted by activated mast cells upon stimulation by them or by CGRP or NT. Proteases such as tryptase secreted by activated mast cells induce the release of inflammatory neuropeptides, for example SP, via PAR-dependent pathways, resulting in an autocrine and/or paracrine mechanism of mast-cell activation with subsequent NGF production besides other inflammatory cytokines (TNF) or vasodilatory molecules (VEGF). Both TNF and NGF might also induce apoptosis, which then diminishes stem cells residing in the bulge area.

Skin stem cells, which are vital for skin homeostasis and self-renewal [63,67], might also be vulnerable to stress. The major epithelial stem cells of the hair follicle are located in its so-called bulge region [63], therefore, it is striking to note that an abnormally high number of apoptotic cells is seen in this hair follicle region after sonic stress, in the immediate proximity of dense, stress-induced perifollicular inflammatory cell infiltrates [7]. Thus, the stress-induced activation of perifollicular mast cells and macrophages might cause substantial, and potentially irreversible, skin damage by upregulation of stem cell apoptosis through the secretion of inflammatory cytokines, such as TNF, IL-1 β and interferon (IFN)- γ .

These findings also have practical implications for animal experimentation. If the profound neuroimmunological effects of auditory psychological stress on test animals are ignored (something that is quite common in animal facilities and in laboratories, yet is notoriously underestimated), this may be the reason why it is frustratingly difficult to reproduce the results of an *in vivo* experiment. Measuring serum corticosterone levels might be a useful index of the stress status of the animals, ideally to be performed in conjunction with simple behavioral and neuroimmune assays.

Pharmacological stress interventions

No specific pharmacological intervention – other than antidepressants and anxiolytics – is currently clinically available to manage selectively the impact of psychological stress on skin disorders in humans. However, reasonable pharmacological treatment options are coming into sight (Table 2). Mast cells could be prominent targets of CRH and related peptides, contributing to neurogenic inflammation; it is therefore reasonable to propose the use of CRHR antagonists [5]. CRHR antagonists (e.g. antalarmin or astressin) would be one class of molecules that could be tested by local administration in the model systems described, especially because higher CRHR-1 gene expression was documented in contact dermatitis [73].

An effective therapeutic intervention, for example, to abrogate stress-triggered telogen effluvium, would have to prolong the anagen phase of the hair cycle, thus preventing the premature onset of catagen, which forms the basis of stress-induced telogen effluvium [64]. External application of the potassium channel opener, minoxidil, to human scalp skin over many months can prolong anagen [74]. It is therefore interesting that topical minoxidil also counteracts the sonic stress-induced, hair growth-inhibitory changes in murine skin effectively *in vivo* [74] (Table 2). Furthermore, SP can be blocked by the application of a high-affinity NK-1R antagonist [7]. However, SP might not be the only, or the main, neuropeptide involved under conditions of stress-induced inflammation because NK-1R, but not SP, are required for stress-induced vascular permeability of the dura mater, suggesting the involvement of some other NK-1 receptor agonist, such as hemokinin [10]. Recently, NGF was identified to act upstream of SP in neurogenic skin inflammation and its receptor antagonists could be used

Table 2. Perspectives in pharmacological stress intervention in skin

Pharmacological intervention	Effect on skin immune response to stress	Species
Topical application of CRHR-1 antagonists [73]	Inhibition of acute stress and CRH-induced skin mast-cell activation and vascular permeability	Rat
Systemic administration of selective NK-1 receptor blocker [7]	Inhibition of stress-induced premature catagen development Diminished occurrence of perifollicular MHC class II cluster Decrease of activated mast cells Note: NK-1R ^{-/-} mice are protected from stress-induced upregulation of SP innervation of the skin, mast-cell activation and stress-triggered patho-physiological patterns of hair follicle apoptosis	Mice
Systemic administration of NGF neutralizing monoclonal antibodies [39]	Inhibition of stress-induced premature catagen development Decrease of pathophysiological patterns of apoptosis in the skin Decrease of SP-positive neurons in spinal ganglia and skin Prevention of mast-cell activation	Mice
Topical application of ATP-sensitive potassium channel opener (minoxidil) [74]	Prevention of stress-promoted premature catagen development Decrease of activated mast cells Decrease of MHC II ⁺ cluster Increase of Ki67 ⁺ proliferating intrafollicular cells (hair bulb)	Mice

for treatment of stress-aggravated skin disorders, such as psoriasis [36] and stress-induced telogen effluvium.

Conclusions

There is now solid evidence for the existence of both a defined 'brain-skin axis', which includes mast cells, NGF and SP [7,39,70], and an intrafollicular equivalent of the central HPA 'stress axis' that includes the production of CRH, ACTH and cortisol [25,26]. One major neuroimmunological research challenge is to elucidate the hierarchical, temporal and spatial interactions of these parameters during central and peripheral responses to psychological stress. Although there are still many more questions than answers, the neuroimmunology of the 'brain-skin connection' during the response to psychological stress is becoming increasingly defined, not the least because of the development of particularly instructive rodent models of stress-induced exacerbation of inflammatory skin conditions and hair growth inhibition. The findings resulting from further exploitation of these models will greatly enrich the current list of candidate molecular targets for clinically useful therapeutic intervention into stress.

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