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CLINICAL IMPLICATION

The "brain–skin connection": nerve growth factor-dependent pathways for stress-induced skin disorders

Emmanouil Zoumakis · Sophia N. Kalantaridou · George P. Chrousos

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Stress can precipitate or exacerbate certain neuroinflammatory manifestations in peripheral tissues, including the skin. Indeed, stress may trigger or aggravate skin diseases, such as atopic dermatitis, psoriasis, urticaria, and alopecia areata or totalis. The precise mechanisms leading to stress-induced or -aggravated skin disorders have just begun to be understood. Thus, recent experimental evidence reveals that distinct neuroendocrine pathways of the brain and the skin are intricately intertwined. This so-called "brain–skin connection" represents an exciting new area of investigation [5]. Mouse models are now available for the detailed mechanistic investigation of the effects of stress on skin diseases.

The stress system in the brain and the periphery includes the hypothalamic–pituitary–adrenal (HPA) axis and the arousal and sympathetic systems (Fig. 1). When activated by stress, the stress system leads to several behavioral, neuroendocrine, autonomic, and immune changes that are part of the adaptive response [1]. Besides the classic stress-related neurohormones of the stress system [corticotropin-releasing hormone (CRH), arginine-vasopressin, adrenocorticotropic hormone, glucocorticoids and the catecholamines norepinephrine and epinephrine], additional mediators, such as nerve growth factor (NGF) and several cytokines, have been identified as important players of the stress response. Circulating NGF levels are increased in patients with inflammatory skin diseases, such as psoriasis [7].

Mast cells are involved in the development of allergic and late-phase inflammation reactions [2]. They are also implicated in nonallergic inflammation, as they release several proinflammatory cytokines, such as tumor necrosis factor and other inflammatory mediators (Table 1). Mast cells are located perivascularly in close proximity to peripheral neuron terminals, including both those of postganglionic sympathetic and sensory [dorsal root ganglia (DRG) neurons] neurons originating in the sympathetic and DRG, respectively (Fig. 1). Skin mast cells produce CRH and express CRH receptors type 1 [4, 6]. They can be activated by many neuropeptides secreted by postganglionic sympathetic and sensory neurons, especially peripheral CRH, substance P (SP), and calcitonin gene-related peptide (CGRP), in response to stress, or by inflammatory mediators. Stress-induced or -aggravated neuroinflammatory skin conditions have been associated with mast cell activation and degranulation. Similarly, we have previously shown that stress induces intracranial mast cell activation, through the sequential action of CRH and sensory neuropeptides [9], and that CRH degranulates skin mast cells and increases vascular permeability [8].

In a murine model of stress involving exposure of C57BL/6 mice to sound stress, Joachim et al. [3] in this issue of the Journal provide evidence that stress, or intracutaneous injection of recombinant NGF mimicking the skin's response to stress, up-regulate the percentage of SP^+ or $CGRP^+$ sensory neurons in skin-innervating DRG

E. Zoumakis · G. P. Chrousos (✉)
First Department of Pediatrics, Choremeio Research Laboratory,
University of Athens Medical School,
Athens, Greece
e-mail: chrousge@med.uoa.gr

S. N. Kalantaridou
Division of Reproductive Endocrinology,
Department of Obstetrics and Gynecology,
University of Ioannina Medical School,
Ioannina, Greece

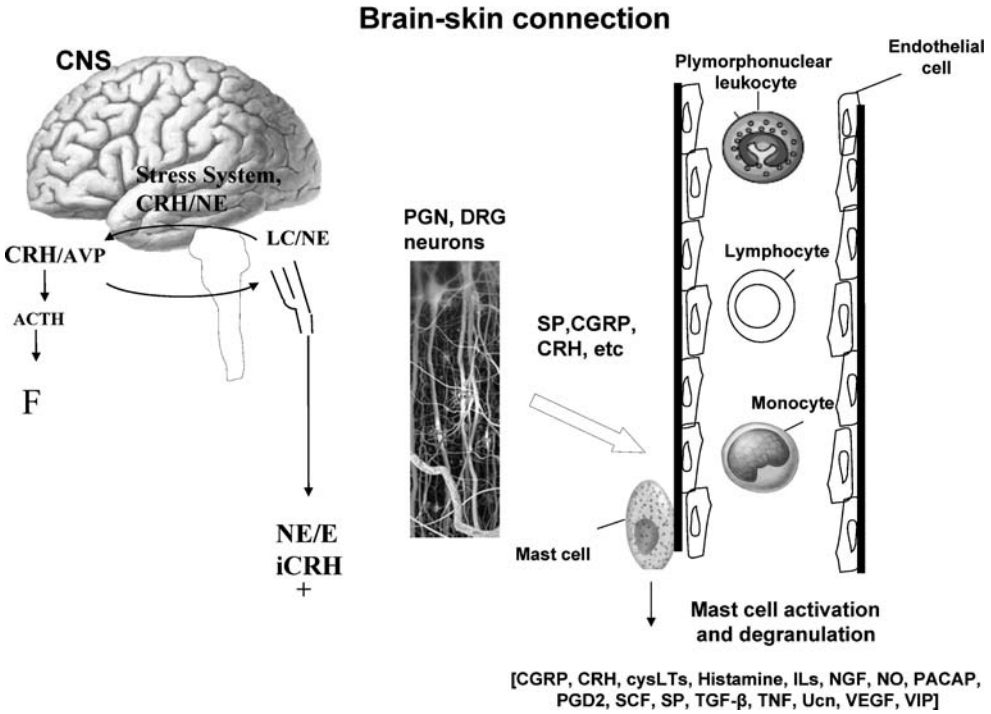

Fig. 1 The stressed brain (*CNS*) exerts its effects on the skin through the stress and sensory afferent systems through endocrine and neural pathways. The first includes effects of the circulating hormones of the HPA axis and sympathetic system, respectively, cortisol (*F*, corticosterone in rodents) and the catecholamines norepinephrine (*NE*) and epinephrine (*E*) on skin cells including mast cells and other immunocytes. The stress system also influences skin targets through the terminals of the postganglionic neurons (*PGN*) emanating from the sympathetic ganglia secreting norepinephrine and a variety of other mediators, including several neuropeptides, such as CRH. The sensory afferent system influences the skin through peripheral nerve fibers emanating from the dorsal root ganglia (*DRG*), also secreting a variety of mediators such as substance P (*SP*)

neurons. They also show that the number of SP^+ or $CGRP^+$ sensory nerve fibers in the dermis of stressed C57BL/6 mice is significantly increased. This means that increased secretion of neuropeptides would be expected, with resultant enhanced local mast cell degranulation and immune cell activation and, hence, inflammation. Furthermore, they demonstrate that neutralization of NGF activity abrogates stress-induced effects on the percentage of SP^+ and $CGRP^+$ sensory neurons in skin-innervating DRG neurons, as well as on dermal sensory nerve fibers. This suggests that NGF plays a major role in the neurogenic component of inflammation and that it is a major mediator of the effects of stress in the skin.

Table 1 Mediators synthesized and secreted during mast cell activation

Mediator
CGRP
CRH
Cysteinyl leukotrienes (cysLTs)
Histamine
Inteleukins (ILs)
NGF
Nitric oxide (NO)
Pituitary adenylate cyclase-activating polypeptide (PACAP)
Prostaglandin D_2 (PGD_2)
Stem cell factor (SCF)
SP
Transforming growth factor-β (TGF-β)
Tumor necrosis factor
Urocortin (Ucn)
Vascular endothelial growth factor (VEGF)
Vasoactive intestinal peptide (VIP)

No target-specific pharmacologic interventions are currently available for the management of stress-triggered or -aggravated skin disorders. The findings by Joachim et al. [3] provide a useful model to conceptualize and generate more effective therapies for these disorders. Thus, abrogation of mast-cell activation, degranulation and local cytokine secretion by blockade of DRG neuron products appears to be a possible area of further investigation for the treatment of stress-related skin disorders. Another possible approach may be the inhibition of the principal stress regulator CRH and peripheral CRH by using CRH receptor type 1 antagonists, such as antalarmin [10]. This small molecular CRH antagonist was previously shown to block CRH-induced mast cell degranulation [9]. Finally, blockade of other stress-related DRG neuron-produced and mast cell-regulating neuropeptides, such as SP, CGRP, or NGF, could be promising areas of research in this direction.

The results reported by Joachim et al. may shed light on the pathophysiology of neuroimmune skin disorders, which are clearly triggered or exacerbated by stress and provide a tool to investigate new treatment strategies for the management of such disorders.

References

1. Chrousos GP (1995) The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation. N Engl J Med 332:1351–1362
2. Elenkov IJ, Chrousos GP (2006) Stress system—organization, physiology and immunoregulation. Neuroimmunomodulation 13:257–267
3. Joachim RA, Kuhlmei A, Dinh QT, Handjiski B, Fischer T, Peters EM, Klapp BF, Paus R, Arck PC (2007) Neuronal plasticity of the "brain–skin-connection": stress-triggered up-regulation of neuropeptides in dorsal root ganglia and skin via nerve growth factor-dependent pathways. J Mol Med DOI 10.1007/s00109-007-0262-6
4. Kempuraj D, Papadopoulou NG, Lytinas M, Huang M, Kandere-Grzybowska K, Madhappan B, Boucher W, Christodoulou S, Athanassiou A, Theoharides TC (2004) Corticotropin-releasing hormone and its structurally related urocortin are synthesized and secreted by human mast cells. Endocrinology 145:43–48
5. Paus R, Theoharides TC, Arck PC (2006) Neuroimmunoendocrine circuitry of the 'brain–skin connection'. Trends Immunol 27:32–39
6. Pisarchik A, Slominski AT (2001) Alternative splicing of CRH-R1 receptors in human and mouse skin: identification of new variants and their differential expression. FASEB J 15:2754–2756
7. Schulte-Herbruggen O, Folster-Holst R, von Elstermann M, Augustin M, Hellweg R (2007) Clinical relevance of nerve growth factor serum levels in patients with atopic dermatitis and psoriasis. Int Arch Allergy Immunol 144:211–216
8. Theoharides TC, Singh LK, Boucher W, Pang X, Letourneau R, Webster E, Chrousos G (1998) Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. Endocrinology 139:403–413
9. Theoharides TC, Spanos C, Pang X, Alferes L, Ligris K, Letourneau R, Roznieckl JJ, Webster E, Chrousos GP (1995) Stress-induced intracranial mast cell degranulation: a corticotropin-releasing hormone-mediated effect. Endocrinology 136:5745–5750
10. Zoumakis E, Rice KC, Gold PW, Chrousos GP (2006) Potential uses of corticotropin-releasing hormone antagonists. Ann N Y Acad Sci 1083:239–251