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Stress, atopy and allergy

A re-evaluation from a psychoneuroimmunologic persepective

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Abbreviations: AD, atopic dermatitis and-like allergic dermatitis; SP, substance P; NK1, neurokinin-1; SPR, SP receptor; HPA, hypothalamic-pituitary-adrenocortical axis; TH, T-helper cell; IL-4 and -5, interleukin (IL)-4 and IL-5; TNFγ, tumor necrosis factor alpha; IFNγ, interferon gamma; $AL(OH)_3$, aluminium hydroxide

Since the early days of psychosomatic thinking, atopic disease was considered exemplary. In the 70s and 80s numerous reports stated increased anxiety, depression or ill stress-coping in atopics in correlation with enhanced disease activity. Employed patient groups however were small and diverse and controls rare. Therefore, the question remained, whether psychopathological findings in atopics were of pathogenetic relevance or an epiphenomenon of chronic inflammatory disease. Recently, the discussion has been revived and refocused by psychoneuroimmunological findings. We now know that atopic disease is characterized by an imbalance of the classical stress-axis response along the hypothalamus-pituitary-adrenal axis (HPA) and the sympathetic axis (SA). This imbalance can be found shoulder-to-shoulder with enhanced expression of newly emerging neuroendocrine stress mediators such as substance P (SP) and nerve growth factor that form up to a third stress axis (neurotrophin neuropeptide axis: NNA). Together they can alter the inflammatory as well as the neuroendocrine stress-response on several levels. In skin, the immediate inflammatory response to stress involves neuropeptide release and mast cell degranulation, in short neurogenic inflammation. Systemically, antigen-presentation and TH2 cytokine bias are promoted under the influence of cortisol and neuropeptides. Imbalanced stress-responsiveness may therefore be at the core of exacerbated allergic disease and deserves re-evaluation of therapeutic options such as neutralization of SP-signaling by antagonists against its receptor NK1, cortisol treatment as supplementation and relaxation techniques to balance the stress-response.

Introduction

The relevance of stress generated by psychological strain such as anxiety, depression, traumatic life events or daily hassles but also by environmental and behavioral factors such as heat, cold, microbes, tobacco smoke, exercise etc., is a matter of hot debate when it comes to development and aggravation of chronic inflammatory diseases. Most clinicians and patients with for example atopic dermatitis will agree that there is some connection and that stress indeed plays a role in the course of the disease.[1] A patient presenting with a demanding job, small children or sick family members to care for, will certainly hear the question: "you do have a lot of stress, don't you?", and if nothing else provides effective treatment, psychotherapeutic or psychoeducational programs may be considered. However, symptoms of neuroendocrine arousal and the immunological results of stress-dependent alterations in neuroendocrine responses are hardly ever discussed or verified. Also stress is always looked at as deleterious and potential beneficial effects especially of dosed exposure are rarely considered.

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Stress and Inflammatory Response: Closely Connected Response Mechanisms to Environmental Change

Like with other chronic diseases, it was not possible to determine a typical atopic personality profile.[2,3] However, our growing understanding of neuronal networks and their lifelong plasticity provides new insights into the hardwiring of neuro-immune interaction and its epigenetic modification beyond genetics and morphogenesis.[4,5] Allergy and psychological aspects are as closely connected to each other as skin and brain, which both derive from the ectoderm. You could say, every neuronal factor ever found to play a role in the brain is also found in functional skin cells (keratinocytes, fibroblasts, etc.,) as well as skin resident (mast cells, Langerhans cells) or skin homing (T-effector cells, antigen presenting cells, macrophages, granulocytes etc.,) immune cells.[6-12] The inflammatory response thereby is the most primitive defense mechanism of the organism and its rudiments developed even before the nervous system. The stress response has developed from the immune response and remained the closely associated and highly conserved oldest response mechanism to environmental changes. Stress has therefore a high potential to

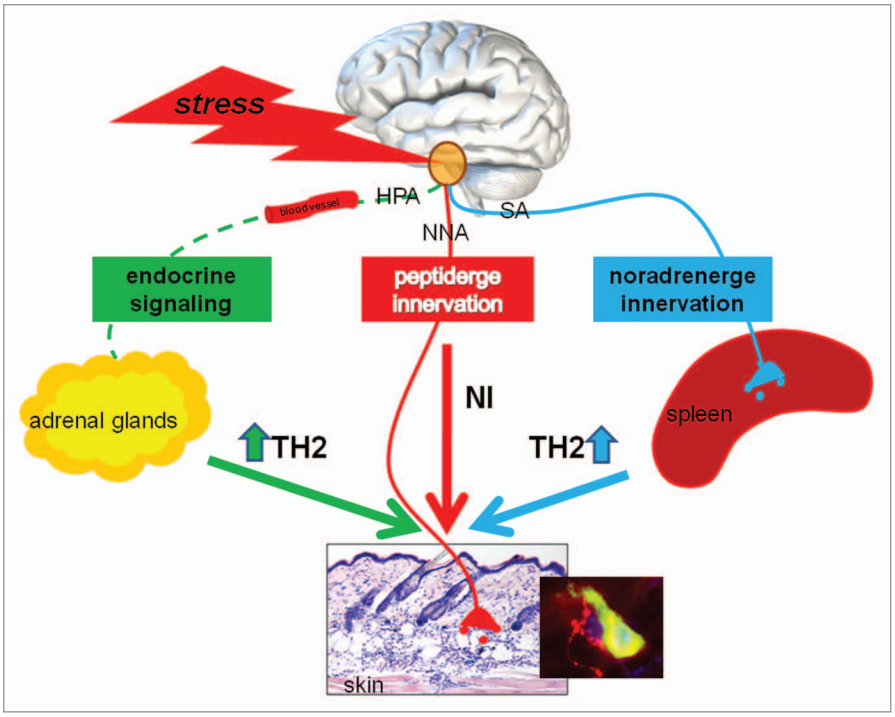

Figure 1. Schematic presentation of neuroendocrine stress effects on skin health. Stress dependent activation of the endocrine pathway (HPA) and the sympathetic nervous system (SA) lead to a systemically TH2 bias, playing a role in the onset and/or extending of the allergic component in atopic diseases. The activation of peptidergic innervations directly effects healthy skin homeostasis inducing TH1 cytokines, mast cells degranulation and eosinophilia leading to a neurogenic inflammation (NI). Understanding of the linkage of these three stress axes—how they communicate with each other and how they influence each other opens the research to future targets of possible disease interventions.

provoke adaptive changes in neuroendocrine-immune circuitry and respective interventions may well be able to improve even genetically determined disease.[13]

A Third Stress Axis Complements Neuro-Immune Adaptation to Inflammatory Challenge

The best known stress pathways commonly are activation of the hypothalamus pituitary adrenal axis (HPA) and the sympathetic axis (SA).[14,15] Acute stress triggers high release of their key mediators cortisol and adrenalin/noradrenalin within minutes. The immune system responds by increased pro-inflammatory cytokine levels such as interferonγ (T helper cell type 1 [TH1] cytokine) and by mounting a fast but tissue damaging cellular immune response.[16,17] By contrast, chronic stress exposure reduces the capacity to mount an acute stress response and increases basal cortisol levels.[15] Now the immune response shifts from cellular to humoral and cytokines such as interleukin 4 and 5 (TH2) are most prominent.[18] This enables the immune system to terminate acute inflammation but also facilitates development of autoimmune and atopic disease.[19,20-24] Interestingly, epigenetic modification of the HPA stress axis renders the individual even more susceptible to mount a misbalanced chronic stress response.[4,25,26]

This simplifying model of the stress response and its immunological effects ignores the presence of a third stress axis that is always co-activated. Along this third stress axis neuropeptides and neurotrophins are released centrally and peripherally (NNA).[11,27-33] Activation of the NNA on the level of the hypothalamus can suppress activation of the HPA axis, a phenomenon described in stressed atopics.[34] In the periphery, neuropeptides released by stress cause massive mast cell degranulation. This activation was first shown by neuroimmunologists such as Bienstock in the 90ies and has been confirmed many times.[11,27-29,31,33,35]

Ever since this discovery review articles stated the pro-inflammatory potential of neurogenic inflammation in the development and aggravation of chronic inflammatory diseases such as atopic dermatitis. Also, skin is growingly recognized as a neuro-immuno-endocrine organ. This organ is not only the target of neuroendocrine mediators but also its source.[36] But the relevance and impact of the cutaneous neuro-immune interaction remained unclear.

Stress during Challenge is Detrimental to Peripheral Inflammation: Evidence from a Mouse Model

In a mouse model for atopic dermatitis-like allergic dermatitis (AlD) and noise stress, as an example of environmental stress that acts through perception of a threat rather than physical harm, we were able to show for the first time, that stress indeed enhances neuronal plasticity and subsequently neurogenic inflammation in a peripheral inflammatory disease. This activation accounted for a worsening of disease parameters such as epidermal hyperplasia, vascular activation or infiltration by eosinophils by approximately 50% and depended on SP and partially on NGF.[11,37] We concluded, that stress around the time of an inflammatory challenge enhances the inflammatory response with deleterious effects on chronic inflammatory diseases.[11,38]

Other have shown that this enhanced neuro-immune interaction also increases the susceptibility of mast cells to respond to non-neuronal mast cell activators such as IgE.[39,40] Intriguingly, this situation may be further enhanced by the chronic-stress-cortisol-release-pattern which results in enhanced SP production by keratinocytes.[41] Other neuropeptides that may contribute to the described immune imbalance include vasoactive intestinal peptide (VIP). Increased levels of this neuropeptide correlate for example with increased IL-4 levels in children of divorced parents.[42]

Interestingly, neurotrophins such as the nerve growth factor NGF are also detectable in increased levels in animals disturbed by

stress on systemic as well as local level.[43-45] Being a neurotrophin, NGF supports enhanced neuro-immune communication by promoting neuronal plasticity but also by directly affecting keratinocyte proliferation and immune cell function in inflamed skin.[46-51] However, activation of this axis does not directly contribute to neurogenic inflammation but rather enhances the skin's level of resistance to any threat imposed upon it.[43]

The Stress Response is not a One Way Street

Summarizing the above, stress appears to be mainly detrimental to chronic inflammatory disease. However, it appears that stress can be trained to handle. Almost 30 years ago for example it was demonstrated that histamin release can be conditioned and mast cell dependent reactions can be modulated by psychoemotional intervention (i.e., hypnosis), which suppresses allergic inflammation.[52-55] Ader was later able to show that it is possible to condition immune suppression via modification of the neuroendocrine stress response.[56] This demonstrates that the stress response is not a one way street that once taken only leads to worsened disease. It can be used to "harden" the organism against repeated challenges. In a recent study, we found that certain stress paradigms enhance neuro-immune interaction with antigen presenting dendritic cells.[57] As a result, T-regulatory cells are produced and suppress cutaneous inflammation in the AlD model.

Neuroimmune Interaction in Lymphoid Organs: High Potential for Systemic Immune Modulation

Some works also suggest that the stress-dependent activation of the noradrenergic innervation of lymphoid organs and subsequently increased production of TH2 cytokines may also play a role in TH2-mediated diseases.[18,58,59] The spleen holds a special position among the lymphoid organ. Primarily noradrenergic innervated with a far smaller portion of peptidergic nerve fibers, the spleen responds to physical and psychological stimulants with a TH2 bias.[60] In addition, Sloan and colleagues showed that social stress in primates lead to increased innervation of lymph nodes in parallel with increased NGF tissue levels and subsequent higher vulnerability to viral infections.[58,61,62]

This splenic TH2 bias is referred to as an anti-inflammatory pathway and protects the body from excessive tissue-destructive, inflammatory response e.g., to an invasion of bacteria, but apparently has also pathogenetic relevance. The amount of cytokines produced within the spleen can act peripherally as well as centrally.[59,63] Like the skin, the spleen has a stress-dependent activated innervation, contacts between nerve fibers and immune cells are an interface between periphery and the CNS.[64-68] It therefore offers itself as an intriguing site to examine the impact of lymphoid neuro-immune interaction and the role of the NNA within it on the onset or prolongation of diseases with allergic and/or inflammatory background.

Future Instructive Directions for the Therapy of Chronic Inflammatory Disease Need to Include Neuroendocrine Circuitry

Targeting the NNA in the treatment of chronic inflammatory disease is a promising target for effective therapeutic intervention. In doing so, the pointed pharmacological intervention to terminate neuro-immune activation in ongoing inflammation by neutralizing SP and/or NGF signaling can complement the classical cortisol therapy. At the same time, any relaxation technique that reduces chronic HPA, SA as well as NNA activation, ranging from laughter to conflict resolving psychotherapy, should prove effective. In analogy to sublingual immunotherapy, which follows the concept of tolerance induction through repeated exposure to minimal allergen challenges, we suggest adopting a popular slogan in establishing therapeutic strategies for the management of allergic disease: "a little stressor a day keeps the doctor away."[69,70] Providing evidence based research and guidelines for future employment of respective therapeutic concepts are important goals of neuroendocrine research in dermatology and it ought to be a primary target of clinical investigation and modern prevention strategies to define therapeutic stress-strategies that break the stress circuit and reestablish a balanced stress response.

In summary, to what degree stress affects inflammatory disease outcome or what pathways are involved is a black box to most patients and doctors. To improve our understanding of the mediators involved has therefore a great potential to optimize handling of chronic inflammatory diseases such as atopic disease and the frustrating treatment of the chronically diseased.[71,72] It should therefore be implemented in standardized patient educational programs and additional pharmacological intervention is to be explored.

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