Stress induced neuroendocrine-immune plasticity
A role for the spleen in peripheral inflammatory disease and inflamming?

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Abbreviations: HPA, hypothalamic-pituitary-adrenocortical axis; SA, sympathetic axis; NNA, neurotrophin neuropeptide stress axis; NA, noradrenaline; CRH, corticotrophin releasing hormone; ACTH, adrenocorticotropic hormone; SP, Substance P; NK1, neurokinin-1 SP receptor; CGRP, calcitonine-gene related peptide; VIP, vasointestinal peptide; TH, T-helper cell; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; MZ, marginal zone; PALS, peri-arteriolar lymphoid sheaths

Research over the past decade has revealed close interaction between the nervous and immune systems in regulation of peripheral inflammation linking psychosocial stress with chronic somatic disease and aging. Moreover emerging data suggests that chronic inflammations lead to a pro-inflammatory status underlying premature aging called inflamming. In this context, the spleen can be seen as a switch board monitoring peripherally derived neuroendocrine-immune mediators in the blood and keeping up a close communication with the central stress response via its mainly sympathetic innervation. The effect aims at balanced and well-timed stress axis activation and immune adaptation in acute peripheral inflammatory events. Constant adjustment to the needs generated by environmental and endogenous challenges is provided by neuroendocrine-immune plasticity. However, maladaptive plasticity induced e.g., by chronic stress-axis activation and excessive non-neuronal derived neuroendocrine mediators may be at the heart of the observed stress sensitivity promote inflamming under chronic inflammatory conditions. We here review the role of neurotransmitters, neuropeptides and neurotrophins as stress mediators modulating the immune response in the spleen and their potential role in inflamming.

Introduction

Neuroendocrine-immune interaction links stress and the immune response and allows individuals to respond to endogenous or exogenous as well as physiological or psychological stressors (Fig. 1). It can take place anywhere where nerve fibers depositing neurotransmitters or neuropeptides meet with cells of the immune system or were blood born neuroendocrine-immune mediators meet with nerve fibers. Respective interaction takes place mainly in peripheral organs at the self-environment interface or in immune-competent tissues such as the spleen.1,4

Lymphoid organs provide the space for differentiation and neuroendocrine modulation of the cells of the immune system passing through them and interacting within.3,6,10 The spleen takes a special position among the lymphoid organs since it is supplied with lymphocytes solely via the blood stream (Fig. 2).11 It is the largest lymphoid organ with the highest lymphocyte throughput of all lymphatic tissues and it is the site of cell pooling, elimination of unneeded cells and regulatory effects on a wide variety of cells of the immune system. High amounts of cytokines are produced by the splenic cells, leaving it via the blood stream and acting centrally and peripherally. The best examined cytokines are interleukin (IL)1, IL6 and Tumor Necrosis Factor α (TNFα).12 At the same time it shows prominent innervation of immune-competent areas as well as altered splenic immunity after central stress mediator blockade.13,14 It is therefore ideally suited to conduct and investigate neuroendocrine-immune communication in loco keeping systemic consequences and their role in chronic inflammation and subsequent inflamming in mind (Fig. 2).

Since receptors for neurotransmitters and neuropeptides as well as neurohormones have been shown on cells of the immune system in the spleen, it is postulated that neural excitation and subsequent secretion or neuronal mediators can directly modulate the immune response in places of close contact.3,35 Vice versa, nerve fibers innervating immune competent tissues carry receptors for neuroendocrine-immune mediators derived from cells of the immune system as well as carried by the blood stream (Fig. 3). They are therefore potentially able to sense and report peripherally derived signals passing through the spleen to the central nervous system.3,5

To dissect the potency of this interaction, we will first introduce the term inflamming and then discuss key neuroendocrine-immune features of the three pillars of the stress response
The Three Pillars of the Neuroendocrine-Immune Response to Stress: SA and the Fight and Flight Response

Historically, the oldest stress axis known is represented by the sympathetic axis (SA). With the discovery of noradrenaline (NA) in peripheral nerve fibers and adrenal derived adrenaline the “fight or flight response” was described by Walter Cannon Bradford. Only later it became evident, that activation of this axis also holds immunological implications: the mediators of the SA are for example responsible for rapid redistribution of the cells of the immune system into the targeted organs upon acute stress activation which supports the fight or flight concept also on the level of local immune defense and promotes rapid microbe or tumor cell elimination in loco. This is further promoted by activation of natural killer cells and TH1 cell differentiation.

The Three Pillars of the Neuroendocrine-Immune Response to Stress: HPA and Its Many Roles in Keeping the Immune Balance

In the fifties of the last century a second stress axis became known and the term stress in its present meaning was coined by Hans Seyle to describe the function of the hypothalamus pituitary adrenal axis (HPA). To date we have learned about a large number of immunological functions of the neuropeptide and endocrine mediators released after activation of this axis such as corticotrophin releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) and cortisol. We know now that depending on secretion mode and amount these neuroendocrine mediators act systemically as well as locally to shape an immune response that is either optimally suited to adapt to acute or to adapt to chronic inflammatory challenges.

Inflammaging: A Premature Aging Process Associated with Stress

To date, the process of aging and why cells lose their capacity to replicate over time is still ill understood. With respect to the immune system, less cells of the immune system are produced and on top show altered functionality such as a reduced capacity to detect neoantigen and a preserved humoral reactivity. In the present literature on unhealthy and premature aging, chronic inflammatory disease plays an important role. The permanent exposure to stressors—endogenous or exogenous, physiological or psychological—during the life span and the individual skill to cope with them tends to provoke chronic inflammation which is summarized under the term inflammaging. A theory that describes how lifelong exposure to stressors meets with the organs declining capacity to neutralize them, which finally results in the incapacity to terminate inflammatory processes. However, it has yet to be comprehensively shown, if an enhanced pro-inflammatory state is cause or result of aging associated chronic diseases. It appears that a systemic dominance of the T helper cell (TH) type 2 immune response associates with aging and thus hints at a potential role for altered splenic immune regulation.

Figure 1. Schematic display of the three stress axis and their activation by a wide variety of stressors as well as selected key effects on the immune system and subsequently chronic disease and inflammaging regulated by inflammatory processes. ‘sympathetic nervous system; ‘hypothalamus pituitary adrenal axis; ‘neurotrophin neuropeptide axis.
neuroendocrine-immune activities of HPA mediators continues to grow daily and the somewhat contradictory results obtained with either acute or chronic stress models continue to confuse, not unlike the diverse functions of the SA.35 The potential role for this stress axis in splenic neuroendocrine-immune regulation is less direct than the role of the SA given the lack of direct neuro-immune interaction in most investigated species.36,37 A stress-modulatory role is nonetheless feasible since cells of the immune system derived from the spleen respond to HPA mediators and are even able to generate some.5,30,34,36

The Three Pillars of the Neuroendocrine-Immune Response to Stress: NNA and Its Potential Anti-Inflammatory Function in the Spleen

Since the 1970s additional stress mediators gradually reveal their presence and role in the stress concert and the existence of a third stress axis can be postulated (Fig. 1).8,38-40 Peripheral nerve fibers including the sensory subpopulation contain neuropeptides with potent immune-modulatory activity and they are subjected to neuronal plasticity guided by neurotrophins. Corresponding to their initial discovery in peripheral nerve fibers, one of the first stress related functions described for this neurotrophin neuropeptide stress axis (NNA) was activation of neurogenic inflammation meaning release of neuropeptides such as substance P (SP) and subsequent degranulation of mast cells in organs at the self-environment border such as the skin, lung or gut.40-45 This innate immune response and the aggravation of chronic inflammatory diseases by its activation were found in virtually every chronic inflammatory disease under the respective scrutiny so far, including atopic/allergic dermatitis. With consequences for TH2 driven inflammation, mediators of the NNA also facilitate the transition to specific immune responses and are involved in TH1/TH2 balance and regulatory cell function.46-51 On first sight though, peptidergic signaling alike the HPA appears to play a minor role in splenic immune function, because of the few respective nerve fibers and contacts detectable and thus little direct neuro-immune interaction.

Neuroendocrine-Immune Interaction in the Spleen is Enabled by Its Dense Innervation

As a prerequisite for the above discussed neuroendocrine-immune interactions taking place in the spleen it is important to understand its neuro-anatomy. The number of lymphocytes and the amount of blood-born neuroendocrine-immune mediators entering the spleen is regulated through the blood flow volume via its sympathetic innervation.52 Noradrenergic nerve fibers represent the vast majority of all splenic nerve fibers and enter the spleen together with the blood vessels.53 Physical as well as psychomotional stress can activate the SA and subsequent release of NA changes the tone of vascular smooth muscle of blood vessels in a receptor-dependent manner thereby redirecting the number of cells passing through the spleen to the peripheral organs.52 About 20% of the noradrenergic nerve fibers innervating the spleen reach beyond the vasculature into the splenic parenchyma.53 The densest innervation is found in the trabecular and the white pulp mostly extending from the blood vessels traveling through them.54 By contrast, the red pulp, where intense phagocytosis takes place, is characterized by basically no innervation.5 This intriguing preference of splenic innervation for the immune competent compartments already suggests neuroendocrine-immune regulatory processes taking place in the spleen.

The respective nerve fiber-immune cell contacts take place mostly in the white pulp, which is the immune-competent area of the splenic parenchyma. It is in the peri-arteriolar lymphoid sheaths (PALS) and the marginal zone (MZ) where the spatial organization of nerve fibers and cells of the immune cells brings them so closely together, that direct interaction is more than feasible.5,53,56 In the PALS nerve fibers contact T-cells and dendritic cells. In the MZ nerve fibers contact macrophages and IgM-positive B-cells. These nerve fibers appear to form direct synapse-like contacts with immune cells which fulfill the criteria for neuro-immune crosstalk.57 In addition to neuroendocrine-immune regulation through regulation of blood flow, a direct splenic neuroendocrine modulation has therefor been postulated for lymphocytes, antigen-presenting dendritic cells and macrophages (Fig. 3). This view is supported by observations such that lymphoid cell outflow is regulated by NA.57

In contrast to the well investigated SA of the spleen, little is known about a potential peptidergic innervation and its influence on neuroendocrine-immune regulation. Only a few publications so far discuss the presence of e.g., SP-containing nerve fibers.58-60 SP and concomitant calcitonin-gene related peptide (CGRP) containing nerve fibers reach the spleen via the central artery, travel along the trabecular system and arborize into the red pulp. In addition they can be sparsely found in the white pulp in the outer PALS in close proximity to T-lymphocytes and in the MZ adjacent to macrophages. Also, very few splenic nerve fibers contain vasointestinal peptide (VIP) and CRH.6,37

Splenic Immune Cells Respond to Neuroendocrine Mediators and Stress by Changing the Cytokine Balance: A Detailed Look

As mentioned above, NA initially promotes the TH1 response. If naïve or CD4+ T-cells are activated in the presence of NA, or T-cell receptor (TCR) activated TH1 cells are exposed to NA, they show higher rates of IFNγ production.61 Also, an acute catecholamine infusion induces proliferation of T-cytotoxic as well as NK cells.26,62 This effect is mostly mediated through α-adrenoreceptors (αAR).63,64 The most abundant receptor for NA on splenic immune cells however is the β2-adrenoceptor (β2AR).31,62,65 TH1 effector cells display a less dense expression of the β2AR within the spleen and reduction of proliferation rates after mitogen.63,64 Through this, cell mediated immune responses are suppressed while TH2 dominance is promoted.66,67

In more detail, the β2AR is expressed by naïve and effector T-lymphocytes but less on B-cells. Corresponding to chronic SA activation, IFNγ production is inhibited if NA is released before TCR is activated (Fig. 3).61

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Despite the apparent lack of prominent direct peptidergic nerve fiber-immune cell interactions in the spleen, some publications discuss the proliferative or suppressive effects of SP on splenic immune cells ex vivo. However, their interest is not the understanding of neuro-immune modification occurring within the spleen but to test the general responsiveness of immune cells to the neuropeptides in question. This is a widely accepted procedure since the spleen is simple to reach and a potent source of large amounts of cells of the immune system for experimental use ex vivo.

Nonetheless, these works demonstrated that SP affects the function of splenic lymphocytes and macrophages, which depends on activation of the neuropeptide 1 receptor (NK1) and SP promotes lymphocyte proliferation of CD4+ T-cells but not B-cells. The supported splenic cell populations appear to be either cytotoxic and acute inflammatory, or regulatory, since SP on the one hand heightens NK cell activity, LFA-1 on CD8+ cells, TNFγ and IgG production, and on the other hand induces expression of CD4 together with CD25 and reduces IgE production. Another neuropeptide, CRH, points in the same direction and promotes splenic TH1 cytokine production as was shown with the help of knockout mice.

In this context, it is important to realize, that cells of the immune system themselves are capable to produce neuropeptides such as SP which can act in a paracrine fashion on cells in their close vicinity. Capsaicin treatment, which depletes and ultimately destroys peptidergic neurons containing e.g., SP, also reduced the amount of detectable sensory neuropeptides in the spleen indicating their in loco production. A notion which is further supported by the observation that CAPS, which regulate the exocytosis of neuropeptide-containing dense-core vesicles, were found in the spleen. Consequently, treatment with capsaicin alters spleen morphology and reduces splenic cell proliferation, NK cell activity and IL2 production as well as CD4/CD25+ T-cell number. With respect to TH1/TH2 balance however, both the production of TH1 and TH2 cytokines were reduced in the spleen.

In addition to the availability of neuroendocrine mediators neuroendocrine-immune regulation is also determined by the length of time and range of diffusion allowed for neurotransmitter and neuropeptide action. This is mainly regulated through the presence and location of enzymes able to terminate their signaling. An enzyme responsible for the digestion of SP is endopeptidase 24.11 (CALLA, CD10, Neprilysin = NEP, CD10/NEP). SP is its preferred substrate but it also digests other tachykinins. It is highly present in histiocytes of lymphatic tissues and may theretofore terminate neuropeptide action in respective areas of the spleen while blocking it results in higher numbers of splenic mature B-cells.

**Splenic Neuroendocrine Interaction Talks Back to the Brain**

Neuroendocrine mediators and cytokines released in the spleen may also have an impact on the activation of the central stress axis, the HPA, since SP as well as pro-inflammatory mediators such as TNFγ or IL1 block HPA activation at the level of the hypothalamus. Vice versa, decreased numbers of noradrenergic neurons in the brain relate to reduced pro-inflammatory cytokine production and cellular immunity in the spleen.

In the central response to leptin CRH acts as a suppressor of splenic immune activation. Also, re-challenge with TH1 inducing LPS results in reduced pro-inflammatory cytokines in the brain but increased in the spleen indicating dissociation between central stress axis activation and peripheral inflammatory response upon rechallenge. These observations indicate that central stress axis activation is intimately linked to splenic immune activation in both directions.

**Stress Response and Pathogenesis of Chronic Inflammatory Diseases**

As mentioned above, since in the late 60s and early 70s, the term stress (meaning the neuroendocrine response of the organism to any threat it encountered which required an adaption of the organisms’ bio-psycho-social functions in order to cope with it) was linked to the development and control of inflammatory disease. The initial experiments demonstrated higher susceptibility to certain viral infections first in stressed mice and then in stressed humans. At the same time it became evident that the immune response can be conditioned in a manner resembling the Pavlov reflex. This conditioning process appears to work through neuro-immune plasticity, an observation that holds important implications for the therapeutic options provided by the analysis and manipulation of the neuroendocrine system in the spleen and can be broadly summarized under the term placebo.

In peripheral organs at the self-environment interface stress-induced neuroendocrine-immune plasticity has been reported a number of times. A social stress- and NGF-dependent change in lymphoid innervation however has been reported only in lymph nodes of primates, where higher density of nerve fibers negatively correlated with IFNy expression and a higher vulnerability to viral infection. A number of disease pathologies however associate with distinct neuroendocrine-immune changes involving the spleen. Especially in aging a TH2 bias of the immune response is observed and associates with altered splenic supply of SA neurons as well as enhanced neuropeptide signaling. The age-related decline of noradrenergic nerve fibers is concomitant with reduced splenic NK-cell activity, declined IL2 and IFNy production and decreased T- and B-cell proliferation. This may explain the observed susceptibility to viral infection and TH2 driven diseases such as asthma bronchiale and autoimmune as in Lupus erythematoses. Independent of aging, other chronic inflammatory autoimmune diseases such as Crohn disease are also associated with neuroendocrine-immune plasticity that hint at pro-inflammatory effects of neuroendocrine-immune states that promote TH1 immunity in cellular dominated inflammatory diseases and those that promote TH2 immunity in humoral dominated inflammatory diseases. Specifically, NA promotes acute and attenuates chronic inflammation in Crohn disease and chemical sympathectomy changes the severity of adjuvant-induced arthritis.
affected patients with psychosocial, medical and economic consequences. Moreover the lesioned skin tends to look prematurely aged. A vicious circle of itching, scratching and subsequent aggravation of the lesions is linked to stress and malfunctioning stress-adaptation as occurring after excessive, uncontrollable and unpredictable biophysical as well as psychosocial stress exposure.

IL4 predominates in the initially developing atopic lesion and contributes to the characteristic TH2 bias. Subsequently, IgE serum levels are increased, vascular cell adhesion molecule (VCAM) is induced on blood vessel epithelia in the skin and eosinophils, mast cells and lymphocytes are recruited into the inflammation site. Approximately 48 h later, the cytokine profile changes and additional IFNγ, the key cytokine of TH1 immune responses, comes into play. At the same time neurotrophin dependent neuronal plasticity occurs in the skin and enhanced numbers of contacts between peptidergic nerve fibers and mast cells as well as dendritic cells alters the susceptibility to stress aggravation and stress intervention.

**Atopic/Allergic Dermatitis: A TH-2 Driven Model Disease for Peripheral Inflammation Tending Inflammaging**

The key symptoms of atopic/allergic dermatitis - pruritus and disfiguring inflammatory skin lesions at visible predilection sites such as the face—greatly reduce the quality of life of the
In summary, as a hub of neuro-immune communication, the spleen is well suited to investigate the effects of stress and subsequent release of neurotransmitters and neuropeptides on the modulation of the immune responses e.g., in chronic inflammatory disease and associated aging processes such as inflammaging. The potential for neuro-immune regulation through this interaction is illustrated by the high number of neuroendocrine responsive lymphocytes that daily circulate through the densely innervated and neuroendocrine active spleen. An immune-modulating effect of stressors that activate the neuroendocrine stress response in the spleen is feasible in both directions: from nerve fibers to cells of the immune system passing through the spleen and from cells of the immune system as well as the circulation to nerve fibers innervating the immune competent areas (Fig. 2). Stress effects in diseases such as atopic/allergic dermatitis, which deteriorate after induction of neurogenic inflammation and TH2 driven inflammation, seem to depend upon the communication between neurogenic and immunogenic components not only in the skin but also in the lymphatics. Mostly however, this has been investigated either on the level of the central stress responses along the HPA and SA or on the level of local neuroendocrine-immune interaction in the affected peripheral tissue and their draining lymphatics. Little attention has been paid to potential guardian role of the spleen.

With this review we hope to have drawn attention to the spleen as a potential switch board between the central and the peripheral stress as well as the immune response with a focus on the NNA. In summary, release of neuronal and/or non-neuronal NNA mediators in the spleen may have an acute pro-inflammatory effect through activation of innate immune responses while on the long run it may promote regulation of inflammation and thereby might conduct inflammaging in peripheral tissues. It therefore complements the neuroendocrine effects of the SA and HPA. By following this idea, we hope to provide insight into potential pathogenic mechanisms of stress-aggravated chronic inflammatory disease in context with inflammaging and to further promote research to develop neuro-immune-modulatory therapeutic strategies in the management of allergic skin diseases and inflammaging.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.
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