Neuroendocrine Effects on Immune System

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INTRODUCTION

The immune system is regulated by a variety of factors ‘from within’: regulatory T cell subsets, cytokines, chemokines, complement, antibodies, *etc* ., and by factors ‘from without’ (a term used by Medawer in 1973): different hormones, neurotransmitters or neuropeptides present in the microenvironment of immunocompetent cells. During an immune response the brain and the immune system “talk to each other” and this process is essential for maintaining *homeostasis* . Thus, the brain and the immune system are the two major *adaptive* systems of the body (1-3).

The central nervous system affects the immune system through the neuroendocrine humoral outflow via the pituitary, and through direct neuronal influences via the sympathetic, parasympathetic (cholinergic) and peptidergic/sensory innervation of peripheral tissues. Thus, circulating hormones or locally released neurotransmitters and neuropeptides regulate major immune functions such as antigen presentation, secretion of cytokines and antibodies, selection of T helper (Th)1 or Th2 responses, lymphocyte activity, proliferation and traffic. Alternatively, certain cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-□, released during an immune response activate the central components of the stress system, alter neurotransmitter networks activity and induce fever, sleepiness, fatigue, loss of appetite and decreased libido. In addition, they activate the hepatic synthesis of acute phase proteins – changes referred to as ‘sickness behavior’ and ‘acute-phase response’, respectively (Figure 1).

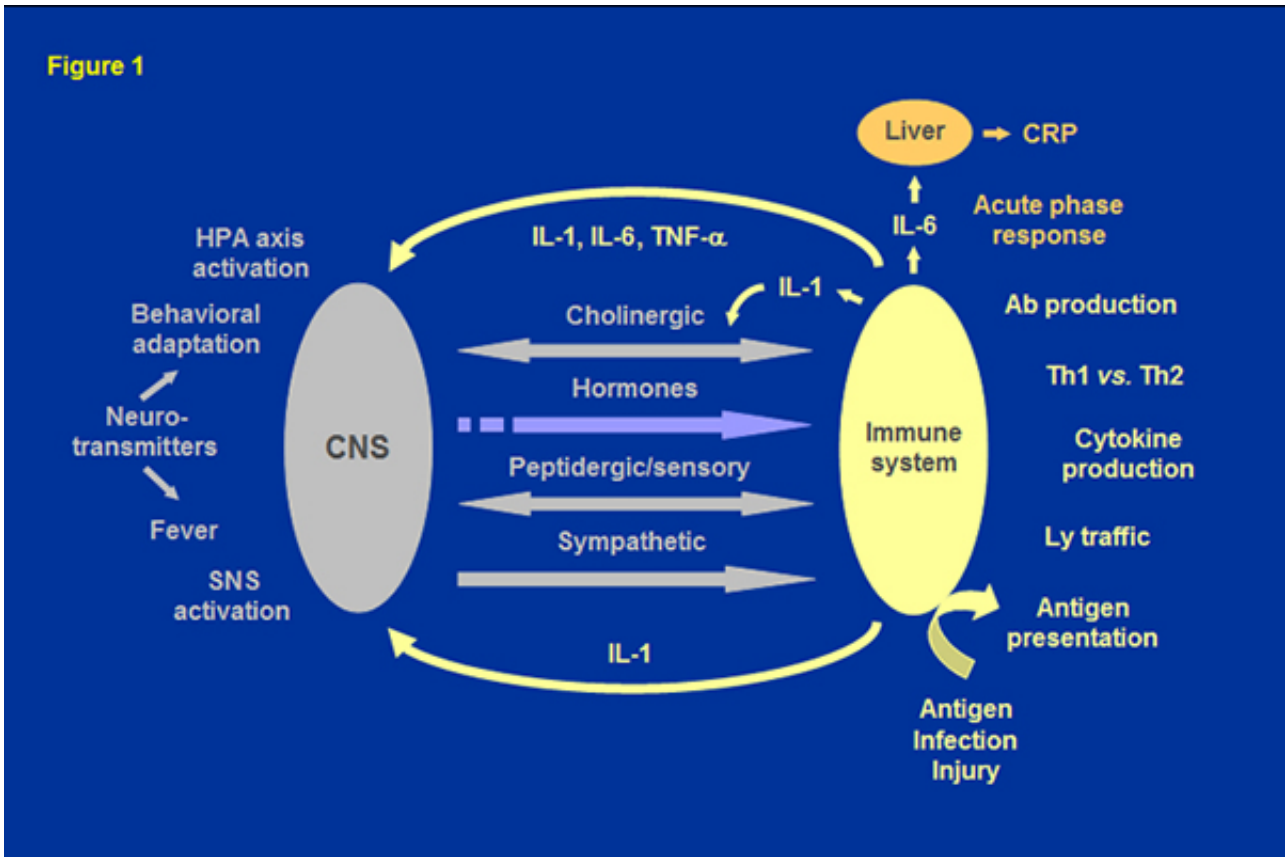

Figure 1.A simplified scheme of the bi-directional communication between the brain and the immune system; role of central and peripheral neuroendocrine and immune adaptive responses triggered by an immune challenge (see text). Lymphoid organs, and particularly their parenchyma, similar to smooth muscles of the vasculature, receive predominantly sympathetic/noradrenergic and sympathetic/neuropeptides Y, and peptidergic/sensory innervation; the heart and the gastrointestinal tract receive both sympathetic and parasympathetic (cholinergic) innervation.Abbreviations: Ab, antibody; CNS, central nervous system; CRP, C-reactive protein; HPA, hypothalamic-pituitary-adrenal (axis); IL, interleukin, Ly, lymphocyte; SNS, sympathetic nervous/adrenomedullary system; Th, T helper cell (response); TNF, tumor necrosis factor.

CYTOKINE PRODUCTION AND Th1/Th2 BALANCE

Immune responses are regulated by antigen-presenting cells (APC) – monocytes/macrophages and dendritic cells (DCs), and by natural killer (NK) cells that are components of *innate immunity* , and by Th lymphocyte subclasses Th1 and Th2, that are components of *adaptive* (*acquired*)immunity. The *innate* immunity provides important instruction that enables the downstream *adaptive* immune responses to select appropriate antigens and the strategies, including the selection of Th1 *vs.* Th2, and cellular *vs* . humoral responses for their elimination. *Homeostasis* within the immune system is largely dependent on cytokines – the immune ‘hormones’ that act

typically in a paracrine fashion to control the proliferation, differentiation and the activity of immune cells. Th1 cells primarily secrete IFN-γ, IL-2 and TNF-α, which promote cellular immunity, whereas Th2 cells secrete a different set of cytokines, primarily IL-4, IL-10 and IL-13 which promote humoral immunity (4-6) (Figure 2).

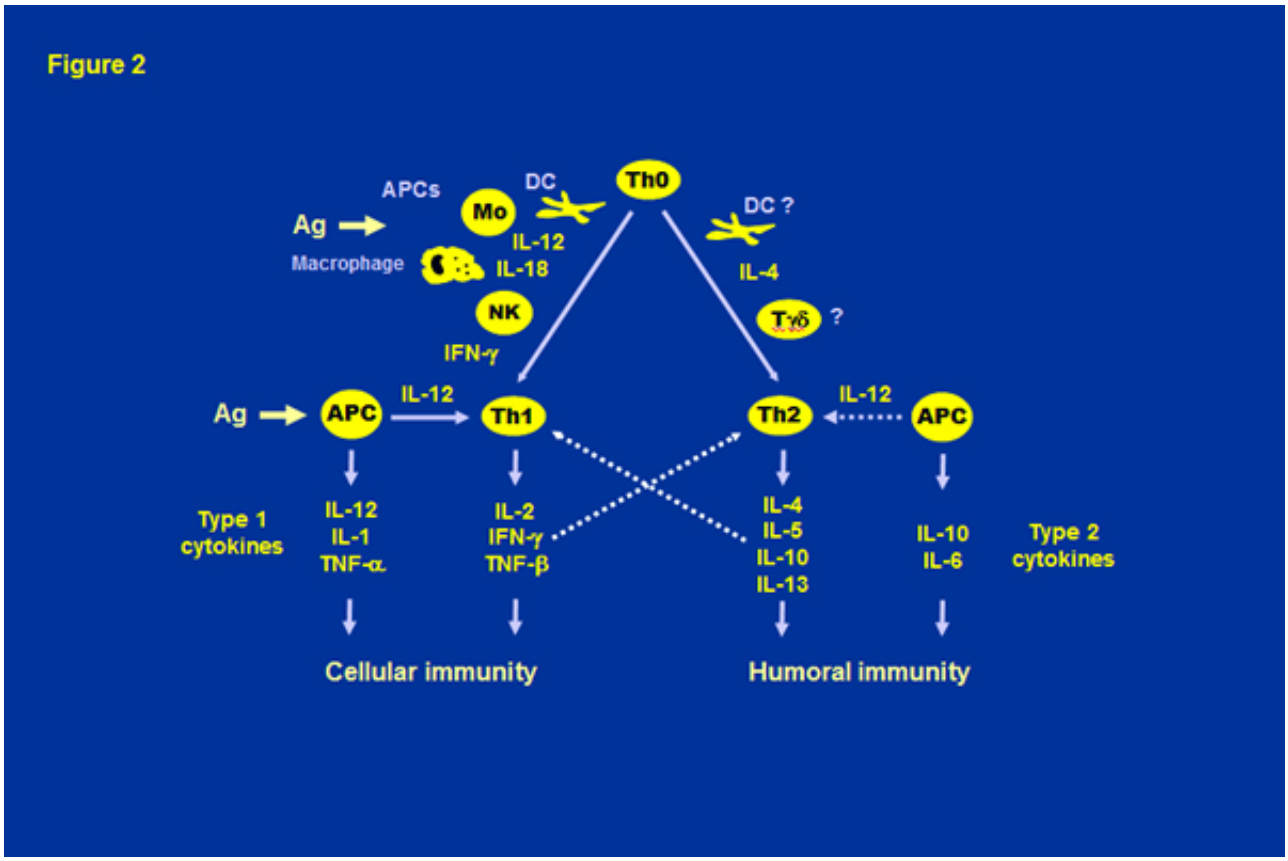

Figure 2.Role of APCs, Th1 and Th2 cells, and type 1/pro-inflammatory and type 2/anti-inflammatory cytokines in the regulation of cellular and humoral immunity. Cellular immunity provides protection against intracellular bacteria, protozoa, fungi and several viruses, while humoral immunity provides protection against multicellular parasites, extracellular bacteria, some viruses, soluble toxins and allergens (see text). The cellular source(s) of IL-4 that directs the differentiation of Th0 cells towards the Th2 phenotype is not well defined. Solid lines represent stimulation, while dashed lines inhibition.Abbreviations: Ag, antigen; APC, antigen-presenting cell; DC, dendritic cell; IFN, interferon; IL, interleukin; Mo, monocyte; NK, natural killer cell; T, T cell (lymphocyte); Th, T helper cell (lymphocyte); TNF, tumor necrosis factor.

Naive CD4+ (antigen-inexperienced) Th0 cells are clearly bipotential and serve as precursors of Th1 and Th2 cells. IL-12, produced by APCs, is the major inducer of Th1 differentiation and hence cellular immunity – in concert with IL-18 and IFN-γ this cytokine promotes Th1 responses (6). IL-12, together with IL-1, TNF-α and IFN-γ stimulate the functional activity of T cytotoxic cells (Tc), NK cells and activated macrophages, which are the major components of cellular

immunity. The type 1 cytokines IL-12, TNF-α and IFN-γ also stimulate the synthesis of nitric oxide (NO) and other inflammatory mediators that drive chronic delayed type inflammatory responses – because of these synergistic roles in inflammation IL-12, TNF-α and IFN-γ are considered the major pro-inflammatory cytokines (4-6).

Th1 and Th2 responses are mutually inhibitory. Thus, IL-12 and IFN-γ inhibit Th2 cells activities, while IL-4 and IL-10 inhibit Th1 responses. IL-4 and IL-10 promote humoral immunity by stimulating the growth and activation of mast cells and eosinophils, the differentiation of B cells into antibody-secreting B cells, and B cell immunoglobulin switching to IgE. Importantly, these cytokines also inhibit macrophage activation, T-cell proliferation and the production of pro-inflammatory cytokines (4-6). Therefore, the Th2 (type 2) cytokines IL-4 and IL-10 are the major anti-inflammatory cytokines.

During the past few years, a novel family of CD4+ Th cells was discovered, which is essentially characterized by IL-17 production and was therefore named 'Th17′. Th17 cells exist both in mice and humans, but their phenotypic and functional features, as well as the mechanisms responsible for their development in the two species, appear to be different. Murine Th17 cells share a common origin with Foxp3+ T regulatory cells, because both populations are produced in response to transforming growth factor-β, but they develop into Th17 cells only when IL-6 is simultaneously produced. Th17 cells in humans differs from that in mice, with IL-1β and IL-23 being the major cytokines responsible for their development. IL-23 is a new heterodimeric cytokine that shares its p40 subunit with IL-12 – it is composed of p40 covalently linked to a p35-related protein p19. Several studies have implicated the IL-23/IL-17 axis in autoimmune inflammation. Interestingly, recent evidence indicates that IL-23 contributes to local inflammation, while IL-12 is mostly involved in systemic responses (7;8).

Glucocorticoids and catecholamines

Studies in the 1970's and the 1980's revealed that glucocorticoids (GCs) and catecholamines (CAs) inhibit lymphocyte proliferation and cytotoxicity, and the secretion of IL-2 and IFN-γ (9;10). These observations, in the context of the broad clinical use of GCs, initially led to the conclusion that stress hormones are, in general, immunosuppressive. Recent evidence indicates, however, that systemically, both GCs and CAs cause selective suppression of cellular immunity and a shift towards Th2-mediated humoral immunity, rather than generalized immunosuppression. This new concept is briefly outlined below.

GCs act through their classic cytoplasmic/nuclear receptors on APCs to suppress the production of IL-12, the main inducer of Th1 responses (11;12). Since IL-12 is extremely potent in enhancing IFN-γ and inhibiting IL-4 synthesis by T cells, the inhibition of IL-12 production by APCs may represent a major mechanism by which GCs affect the Th1/Th2 balance. Thus, GCs-treated monocytes/macrophages produce significantly less IL-12, leading to their decreased capacity to induce IFN-γ production by antigen-primed CD4+ T cells. This is also associated with a down regulation of the expression of IL-12 receptors on T and NK cells and an increased production of IL-4 by T cells (11-14), (see Figure 2 and Figure 3).

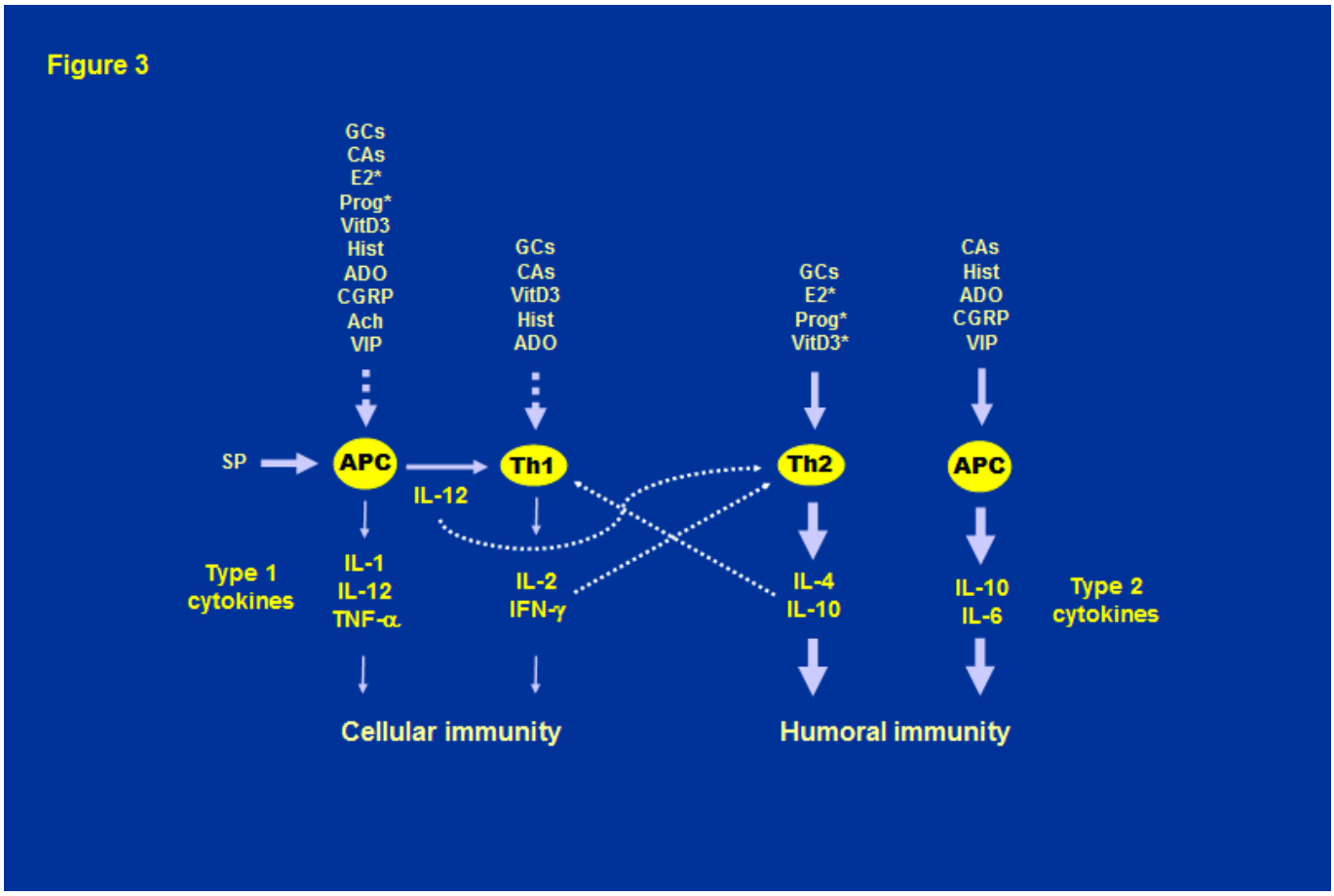

Figure 3.Effects of different hormones, neurotransmitters or neuropeptides on type 1/pro-inflammatory and type 2/anti-inflammatory cytokine production, the Th1/Th2 balance, and cellularvs. humoral immunity. Note that the systemic Th2-inducing, anti-inflammatory effects of some hormones and neurotransmitters, as depicted here, may not pertain to certain conditions or local responses (see text and Figure 4, below). GCs, E2 and 1,25(OH)2 vitamin D3 do not affect the production of IL-10 by monocytes; yet, lymphocyte-derived IL-10 production is up-regulated by these hormones. *Available evidence suggests that progesterone up-regulate the production of IL-4 by lymphocytes and Th2 cells, without affecting the secretion of IL-10 by these cells; conversely, E2 and 1,25(OH)2 vitamin D3 up-regulate lymphocyte-derived IL-10, but do not affect the production of IL-4. Note that CAs, and probably histamine and adenosine are not able to affect the production of type 2 cytokines by Th2 cells, directly, simply because these cells do not express b2-ARs, and most likely H2 and A2a receptors or because Th2 cells might have less active cAMP/PKA pathway. Indirectly, however, andin vivoconditions, they may potentiate the cytokine production by Th2 cells, since they remove the inhibitory restraints on these cells exerted mainly by IL-12 and IFN-g. Solid lines represent stimulation, while dashed lines inhibition.Abbreviations: Ach, acetylcholine; ADO, adenosine, CAs, catecholamines, CGRP, calcitonin gene-related peptide; GCs, glucocorticoids, E2, estradiol; IL, interleukin; IFN, interferon; NE, norepinephrine; Prog, progesterone; SP, substance P; TNF, tumor necrosis factor; VIP, vasoactive intestinal polypeptide, VitD3, 1,25(OH)2 vitamin D3.

In contrast to CAs, GCs also have a direct effect on Th2 cells by up-regulating their IL-4, IL-10 and IL-13 production (12;15). GCs do not affect the production of IL-10 by monocytes (11;16); yet, lymphocyte-derived IL-10 production is up-regulated by GCs (15). This could be the result of a direct stimulatory effect of GCs on T cell IL-10 production and/or a block on the restraining inputs of IL-12 and IFN-γ on lymphocyte IL-10 production.

The two major CAs, norepinephrine (NE) and epinephrine, through stimulation of □□-adrenergic receptors (ARs) potently inhibit the production by APCs of IL-12, and, thus, they inhibit the development of Th1-type cells, while promoting Th2 cell differentiation (11;17;18). CAs also inhibit the production of TNF□□ by monocytes, microglial cells and astrocytes, and suppress the production of IL-1, an effect that is mostly indirect via inhibition of TNF□□ and potentiation of IL-10 production (19-23).

While suppressing type 1 cytokine production, CAs upregulate the production of type 2 cytokines by APCs. Thus, the production of IL-10, one of the most potent anti-inflammatory cytokines, is potentiated by NE and epinephrine, an effect which is □□-AR-mediated and cAMP-PKA-dependent (11;24). Similarly, the production of IL-6, a cytokine that exerts both pro- and anti-inflammatory effects, but possesses mostly Th2-type activities (previously known as BCDF, B cell differentiation factor) is also up-regulated by CAs (25;26).

It appears that □2-ARs are expressed on Th1 cells, but not on Th2 cells (27). This may provide an additional mechanistic basis for the differential effect of CAs on Th1/Th2 functions. In fact, in both murine and human systems, □□-AR agonists inhibit IFN-γ production by Th1 cells, but do not affect IL-4 production by Th2 cells (27;28). Pre-treatment with the □□-AR agonists salbutamol in mice also induces an increase of the *ex vivo* release of IL-4, IL-6 and IL-10 (29) – most likely an indirect effect, due to the removal of the inhibition by IL-12 and IFN-γ on Th2 cells (see Figure 2 and Figure 3).

Recently we reported that in a large subpopulation of healthy humans the baseline epinephrine output (but not cortisol and sex steroid hormones) correlated inversely with proinflammatory and positively with anti-inflammatory cytokine production. Thus, low vs high epinephrine excretors had a 2- to 5-fold higher TNF-α and IL-12 production but 2-fold lower IL-10 production induced by LPS ex vivo. This indicates that baseline epinephrine conditions cytokine responsiveness and through this mechanism intrinsic hypo- or hyperactive adrenal medullas in some individuals may shape opposite cytokine profiles (30).

NPY

Sympathetic/neuropeptide Y (NPY)-positive nerve fibers predominantly supply the vasculature, where they mainly occur as perivascular plexuses and both NE and NPY, released from these fibers control blood flow and lymphocyte traffic. They branch off only rarely to run into the lymphoid parenchyma (31). NPY is co-released with NE upon sympathetic nervous system (SNS) activation – particularly in conditions of high sympathetic activity large dense-cored vesicles release both NPY and NE (32). NPY does not usually act as a genuine co-transmitter but rather as a pre-junctional or post-junctional modulator of the release or the effects of the

principal transmitters, NE and ATP. In many tissues the major action of NPY is to enhance the post-junctional response of NE and ATP.

NPY inhibits IL-6 release from splenic macrophages via stimulation of the Y1 receptor. NPY also potentiates CAs-induced inhibition and stimulation of IL-6 production by these cells through α2- and β2-ARs, respectively (33). In the presence of NPY differentiated Th1 cells produce less IFN-γ, but Th2 cells express an increased IL-4 production. Additionally, administration of NPY induces an inhibition of the *ex vivo* production of IFN-γ in antigen-specific murine lymphocytes. Thus, NPY similar to CAs might possess Th2-inducing properties (34).

ATP

In many tissues ATP is co-stored with NE and NPY in the sympathetic nerve terminals (35). The sympathetic nerves most likely release ATP transiently, only at the beginning of a train of nerve stimulation. The release of NE occurs later in the train and, once started, is maintained throughout the course of nerve stimulation (36). In blood vessels, ATP is particularly abundant, and the proportion ATP to NE is extremely variable in different blood vessels beds. Once released ATP is rapidly breakdown to adenosine (ADO) by extracellular nucleotidases (35;36). Ischemic-like condition releases both NE and ATP in the rat spleen (37), further studies, however are needed to clarify the release of ATP and its source in lymphoid organs, under more physiologic conditions.

ATP, like CAs might favor Th2 responses, through stimulation P2Y11 receptors and subsequent increase of cAMP. This is mediated through an inhibition IL-12p70 and TNF-α, and stimulation of IL-10 production by APCs (38;39). As a result, T cell lines generated from allogeneic naive CD45RA(+) T cells primed with DCs matured in the presence of ATP produce lower amounts of IFN-γ and higher levels of IL-4, IL-5, and IL-10 (40). Recent evidence indicates that ATP enhances the expression of IL-23 by human monocyte-derived DCs. Interestingly, the reciprocal regulation of IL-12 and IL-23 by ATP is mediated by 2 distinct P2 receptors – the inhibition IL-12p70 is mediated by P2Y11 receptors, while the up-regulation of IL-23 is most likely mediated by P2Y1, P2Y2, P2Y12 or P2Y13 receptors, which are all expressed by monocyte-derived DCs (41).

The P2X7 receptor belongs to the 2PX family of ligand-gated ion channels and is restricted to monocytes, macrophages, microglial cells, and some lymphocytes and cancer cells. Ligation of the P2X7 receptor activates proIL-1β post-translational processing resulting in increased release of IL-1β by monocytes and microglial cells (42;43). ATP also enhances IL-18 production by monocytes, but inhibits TNF-α production. IL-18, like IL-1β is produced as a propolypeptide that requires cleavage by caspase-1 to generate an active mature cytokine. Thus, it appears that ATP via stimulation of P2X7 receptor can act as an extracellular initiator of the post-translational processing of certain pro-inflammatory cytokines, such as IL-1β and IL-18 (42;43). Interestingly, extra cellular ATP, released during hypoxia, ischemia or inflammation has been recently proposed to represent an endogenous ‘danger’ signal that activates dendritic cells through the P2X7 receptor (44;45).

Adenosine

In addition to the release from postganglionic sympathetic nerve terminals (see above), during inflammation, ischemia and tissue injury intracellular ATP metabolism is accelerated, resulting in an enhanced release from metabolically active cells of the endogenous purine nucleoside adenosine (ADO). ADO exerts potent anti-inflammatory and immunosuppressive effects mediated mainly by A2 receptors: diminished leukocyte accumulation, inhibition of complement (C2) production, and reduction of the superoxide anion generation (46-48). ADO through stimulation of A2a receptor- cAMP/PKA pathway also inhibits IL-12 and TNF-□ production by human monocytes (49;50). ADO potentiate, however, the production of IL-10 by APCs (49;51;52). This indicates that ADO expresses a Th1/Th2 modulatory profile similar to CAs and histamine (Figure 3).

Estrogen and progesterone

Estradiol (E2), similarly to GCs does not affect the production of IL-10 by monocytes (53;54); yet, lymphocyte-derived IL-10 production is up-regulated by E2 (Figure 3). In the presence of high doses of E2 the majority of the antigen-specific T cell clones show enhancement of antigen- and anti-CD3- stimulated human IL-10 production (55-57). This is relevant to the finding that E2 may polyclonally increase the production of IgG, including IgG anti-dsDNA, in systemic lupus erythematosus (SLE) patients' peripheral blood mononuclear cells (PBMC) by enhancing B cell activity and by promoting IL-10 production – evidence that supports the involvement of E2 in the pathogenesis of SLE (58). E2 also decreases LPS-induced TNF□□ production by inhibition of the transcription factor NF-kappa B (53;56;57). E2 might exert biphasic effects on secretion of TNF□□, with enhancement occurring at low doses of E2, and inhibition at high concentrations (53;56;59). E2 does not affect the production of IL-12 by murine splenic macrophages, CD11c+ splenocytes and human monocytes, but up-regulates IL-12 production in bone marrow-derived dendritic cells (53;54;60). However, CD11c+ splenocytes isolated from animals with supplemental E2 produce more IFN-γ in response to IL-12 and IL-18 (60). These data illustrate that E2 has differential effects on the development and function of DCs and IFN-producing killer DCs (IKDCs). Thus, E2 may strengthen innate immunity by enhancing IFN-γ production by CD11c+ cells, and this observation may provide a key mechanism regulating differences in the prevalence of autoimmune diseases and susceptibility to infection between sexes.

Progesterone also favors the Th2 development mainly through induction of IL-4 and IL-5, and through inhibition of TNF-α□production. Progesterone decreases steady state levels of TNF□□ mRNA and the production of intracellular and secreted TNF□□ (61). Importantly, progesterone, at concentrations comparable to those present at the materno-fetal interface, induces the development of Ag-specific CD4+ T cells lines and clones that show enhanced ability to produce IL-4 and IL-5, without affecting the secretion of IL-10 (55;62). Moreover, progesterone also induces the expression of IL-4 mRNA and production in established human Th1 clones (62). Estrogens and progesterone are most likely to drive a substantial Th2 shift only at concentrations (up to 35 000 pg/ml) associated with pregnancy (55).

Some of the actions of estrogens, might be indirect rather than direct on cytokine producing

cells. Estrogen enhances the activity of the stress system (63). The CRH gene contains a functional estrogen-responsive element and E2 decreases corticosteroid receptor levels in the hypothalamus, the anterior pituitary, and the hippocampus, resulting in decreased corticosteroid feedback (63;64). Estrogens are also potent inhibitors of the extraneuronal uptake of norepinephrine (uptake-2) (65). Thus, estrogens, via an increase of systemic and local levels of CAs and cortisol are probably able to amplify their effects on Th1/Th2 balance (see also clinical implications).

Interestingly, an estrogen deficiency has been linked to induction of bone loss by enhancing T-cell production of TNF□□ (66). The differentiation of cells of the monocytes lineage into mature osteoclasts is specifically induced by TNF-related factor, RANKL (receptor activator of NF-kappaB ligand). T cells from ovariectomized mice produce increased amounts of TNF, which augments RANK-induced osteoclastogenesis (67). This evidence indicates that the enhanced T cell production of TNF resulting from increased bone marrow T cell number might represent a key mechanism by which estrogen deficiency induces bone loss in vivo (67;68).

1, 25-Dihydroxyvitamin D3

1,25(OH)2 vitamin D3 preferentially targets Th1 activity by inhibiting the secretion of both IFN-□ and IL-2 and by suppressing the production of the pro-Th1 cytokine IL-12 by APCs (69). The hormone inhibits IL-12 production by activated macrophages and DCs by down regulation of NF-kappaB activation and binding to the p40-kappaB sequence (70). 1,25(OH)2 vitamin D3 has little or no effect on IL-4 production but enhances IL-10 secretion by DCs and IL-10 and IL-5 by PBMC (71-73). Similarly to GCs 1,25(OH)2 vitamin D3 up-regulate lymphocyte-derived IL-10, but do not affect the production of IL-10 by monocytes. Thus, 1,25(OH)2 vitamin D3 may selectively inhibit Th1 functions, and favor Th2 responses. Therefore, the development of less hypercalcemic analogs of 1,25(OH)2 vitamin D3 might open a new therapeutic area in autoimmunity and organ transplantation. In fact, it has recently been shown that administration of such analogs by inhibiting IL-12 and Th1 development prevents or ameliorates chronic-relapsing experimental allergic encephalomyelitis (EAE) and autoimmune diabetes in mice (74;75). In addition, the clinical improvement in psoriasis after application of calcipotriene, a synthetic analog of 1,25(OH)2 vitamin D3 has been linked to the reduction of IL-8 and the increase of IL-10 production, induced by this drug (76)

Histamine

Histamine, through activation of H1 histamine receptors is one of the major mediators of acute inflammation and allergic reactions. Histamine, however, via stimulation of H2 receptors expressed on immune cells also exerts important immuno-regulatory functions (77). Thus, histamine inhibits IL-12 and TNF□□, but potentiates IL-10 and IL-6 production by human monocytes and DCs (78-81). In addition, histamine, via H2 receptors inhibits IFN-□ production by Th1-like cells, but has no effect on IL-4 production from Th2 clones (82). Thus, histamine, similarly to CAs, appears to drive a Th2 shift at the level of both APCs and Th1 cells (Figure 3). Through this mechanism allergen/antigen-IgE-induced-release of histamine might participate in a positive feedback loop that promotes and sustains a shift to IgE production in topic/allergic

conditions.

Peptidergic/sensory nerves

Lymphoid organs and blood vessels receive predominantly sympathetic/neuropeptide Y and peptidergic/sensory innervation. The most abundant peptides are substance P (SP) and cacitonin gene-related peptide (CGRP) closely overlapping anatomically, but not necessarily co-localized in the sensory innervation, and vasoactive intestinal polypeptide (VIP), present in the cholinergic innervation (see below). SP and CGRP are widely distributed in the central nervous system and the gastrointestinal tract. CGRP is also abundant in the cardiovascular and the urogenital systems, the thyroid gland and the skin. Whereas SP stimulate most macrophage functions and upregulates TNF□□ and IL-12 production by monocytes and macrophages, CGRP down-regulates pro-inflammatory TNF□□ and IL-12 production, but potentiates IL-6 and IL-10 secretion through the CGRP1 receptor-cAMP/PKA pathway (83-88). In addition, both SP and CGRP are strong vasodilators, CGRP being the most potent vasodilator yet discovered.

Parasympathetic (cholinergic) system

Activation of afferent vagus nerve fibers by cytokines is known to stimulate the HPA axis (89-91). Recent evidence indicates that the efferent vagus nerve signaling is involved in immunoregulation. Thus, exposure of human macrophages, but not peripheral blood monocytes to acetylcholine (Ach), the principal vagal neurotransmitter or to nicotine inhibits the release of pro-inflammatory cytokines TNF□□, IL-1 and IL-18, without affecting the anti-inflammatory cytokine IL-10 in response to endotoxin (92;93). Macrophage cholinergic receptor activity is exclusively sensitive to □-bungarotoxin, implicating nicotinic-type receptor activity in the transduction of the cytokine-inhibiting signal. Moreover, direct electrical stimulation of the peripheral vagus nerve, *in vivo,* during experimental endotoxaemia in rats suppresses TNF□□ synthesis in liver and heart, attenuates peak serum TNF□□ levels, and prevents the development of endotoxic shock. These observations suggest the presence of parasympathetic/cholinergic anti-inflammatory pathway by which the brain may modulate inflammatory responses (92;93). In addition to the VIP-ergic innervation of the lymphoid organs, activated T cells, and particularly Th2 cells are the major VIP source in the immune system (88). VIP inhibits TNF□□ and IL-12 production, and stimulates the secretion of the anti-inflammatory cytokine IL-10, primarily through VPAC1 receptors on immune cells (88). However, VIP induces marked vasodilatation in most vascular beds. Recent evidence indicates that the immunosuppressive effect of VIP may also involve the generation of antigen-specific regulatory T cells (Treg) through the induction of tolerogenic dendritic cells (tDC). The VIP $\rightarrow$ tDC $\rightarrow$ Treg axis contributes to the beneficial effects of VIP in models of autoimmunity, and could represent a new therapeutic approach for the treatment of autoimmune diseases (94).

Local vs. Systemic Effects

The systemic Th2-inducing properties of several hormones may not pertain to certain conditions or local responses in specific compartments of the body. Thus, GCs treatment results in a significant increase of the number of IL-12+ cells with concurrent reduction in the number of

IL-13+ expressing cells in bronchial biopsy speciments of asthmatics. Interestingly, this occurs only in steroid-sensitive but not steroid-resistant asthmatic subjects (95). The number of IL-4+ cells in the bronchial and nasal mucosa is also reduced by glucocorticoid treatment (96;97). Furthermore, the synthesis of transforming growth factor (TGF)-β, another cytokine with potent anti-inflammatory activities, is enhanced by GCs in human T cells but suppressed in glial cells (98), and low doses of GCs can indeed activate alveolar macrophages, leading to increased LPS-induced IL-1β production (99).

Moreover, NE, via stimulation of □2-ARs can augment LPS-stimulated production of TNF□□ by mouse peritoneal macrophages (100). In rodents, induction of hemorrhage, a condition associated with elevations of systemic CAs concentrations or exposure of to mild inescapable electrical foot shock stress results in increased IL-1□ and TNF□□ production by alveolar macrophages and lung mononuclear cells (101;102). These effects are most likely indirect – *in vitro,* a direct modulatory effect of CAs on LPS-induced IL-1□ by alveolar macrophages was not demonstrated. Thus, the stress-induced changes in alveolar macrophage activity might result from alveolar type II epithelial cell activation, leading to release of surfactant and/or other factors (102).

CAs also potentiate the production of IL-8 (a chemokine that promotes the recruitment of polymorphonuclear cells to an inflammatory site) by monocytes, epithelial cells of the lung and endothelial cells, indirectly, via an effect on platelets (103-106). Furthermore, CAs (through □2/□3-ARs) and insulin up-regulate IL-6 production by human adipocytes (107;108). IL-6 is the major inducer of C-reactive protein (CRP) production by the liver and both GCs and CAs enhance this induction to a greater or lesser extent (109). Interestingly, histamine induces the production of both IL-6 and IL-8 by coronary artery endothelial cells, whereas chronic □-AR stimulation induces myocardial, but not systemic, elaboration of TNF-□, IL-1□ and IL-6 (110;111).

CRH/SP-mast cell-histamine axis

Peripherally produced CRH acts as a local auto/paracrine proinflammatory agent (*peripheral* or *immune* CRH) (112). Immunoreactive CRH is identified locally in experimental carrageenin-induced subcutaneous aseptic inflammation, streptococcal cell wall- and adjuvant-induced arthritis, and in human tissues from patients with rheumatoid arthritis (RA), autoimmune thyroid disease and ulcerative colitis. CRH may be produced locally by immune cells but also delivered to inflamed tissues by peripheral nerves (112;113). Peripheral CRH has vascular permeability-enhancing and vasodilatory actions. CRH administration causes major peripheral vasodilatation manifested as flushing and increased blood flow and hypotension (114). An intradermal CRH injection induces a marked increase of vascular permeability and mast cell degranulation, mediated through CRH-R1 (115). It appears that the mast cell is a major target of immune CRH. This concept has an anatomic prerequisite: in blood vessels and the lymphoid parenchyma plexuses of nerve fibers (noradrenergic and peptidergic) are closely associated with clusters of mast cells (cf. Ref. 3). SP and peripheral CRH, which are released from sensory peptidergic neurons, are two of the most potent mast cell secretagogues (115-118).

Thus, peripheral CRH and SP activates mast cells via a CRH type 1 and NK1 receptor-dependent mechanism leading to release of histamine and other contents of the mast cell granules that subsequently may cause vasodilatation, increased vascular permeability and other manifestations of inflammation. Therefore, the activation of CRH/SP-mast cell-histamine axis through stimulation of H1 receptors may induce acute inflammation and allergic reactions, while through activation of H2 receptors it may induce suppression of Th1 responses and a Th2 shift. This adds further complexity to the local effects of hormones, neurotransmitters and neuropeptides; in conjunction with local mediators of inflammation (see Figure 4).

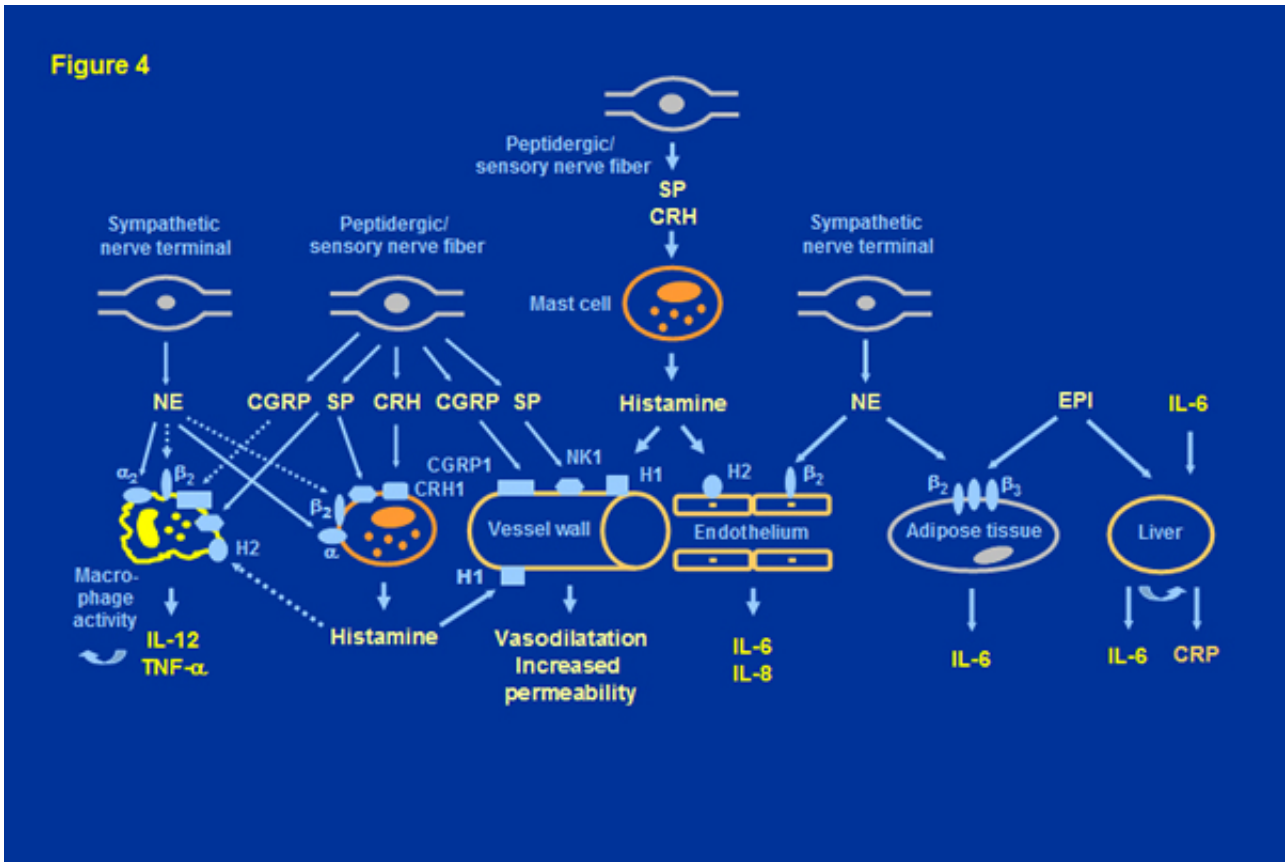

Figure 4. Simplified scheme of the complex interactions between CAs, neuropeptides and the CRH/SP-mast cell-histamine axis, and their pro- and anti-inflammatory effects in certain local responses (see text). Solid lines represent stimulation, while dashed lines inhibition.Abbreviations: CGRP, calcitonin gene-related peptide; CRH, corticotropin-releasing hormone (peripheral); EPI, epinephrine; IL, interleukin; NE, norepinephrine; SP, substance P; TNF, tumor necrosis factor.

ANTIGEN PRESENTATION

For T cells to be optimally activated, recognition of antigen/major histocompatibility complexes (MHC) by the T-cell receptor (TCR) must be accompanied by a second co-stimulatory signal.

This co-stimulatory signal is predominantly generated by B7.1 and/or B7.2 molecules, expressed on APCs, when engaged to their counter-receptor, CD28, present on T cells. GCs inhibit the expression of B7.1 and B7.2 in human monocytes and DC, respectively, and down-regulate MHC II expression in APCs. 1,25(OH)2 vitamin D3 and CGRP decrease B7.2 expression and MHC II, without affecting B7.1, while VIP reduces the expression of both B7.1 and B7.2 in activated macrophages. The down-regulation of B7 and MHC II molecules may contribute to the inhibitory effects of these hormones and neuropeptides on APC-dependent T-cell activation (86;88;119-121).

The Toll-like receptors (TLRs) recognize conserved microbial products – TLR-4 and TLR-2 mediate the host response to Gram-negative and Gram-positive bacteria, respectively. Stimulation of Toll-like receptors by microbial products leads to the activation of signaling pathways that result in the induction of inflammatory and antimicrobial innate immune responses. Recent evidence indicates that GCs induce TLR-4 in the resting condition, yet after T cell activation they decrease TLR-4 expression (122).

Lymphocyte Traffic and Proliferation

After a single dose of a short-acting glucocorticoid, the concentration of neutrophils increases, whereas the lymphocytes (T and B cells), monocytes, eosinophils, and basophils in the circulation decrease in number. The increase of neutrophils is due both to the increased influx from the bone marrow and to the demargination and impaired extravasation of neutrophils. The decreased migration of neutrophils from the blood vessels combined with diminished chemotaxis and adherence to vascular endothelium of neutrophils and monocytes results in inhibition of the accumulation of these cells at the site of inflammation. These effects underlie the potent anti-inflammatory properties of GCs. The reduction in circulating lymphocytes, monocytes, eosinophils, and basophils is the result of their movement from the vascular bed to lymphoid tissue.

Two phases are recognized after CAs administration in humans: a quick (<30 min) mobilization of lymphocytes, followed by an increase of granulocytes with relative lymphopenia (maximal response at 2-4 h) (123). CAs predominantly affect NK cells and granulocytes circulation, whereas T- and B-cell numbers remain relatively unaffected. Infusion of both NE and epinephrine in humans results in marked increases (between 400-600%) of NK cell numbers (CD16+CD56+), most probably due to the □2-AR-mediated demargination of NK pool in blood vessels. By contrast, a reduction of NK cell number is observed after 7 days of treatment with terbutaline, a □□-AR selective agonist, changes identical to that seen in congestive heart failure patients (124). Thus, in the short term, CAs acutely mobilize NK cells from depots, whereas in the long term, chronically, CAs decrease the number of lymphocytes, and particularly of NK cells in the peripheral blood.

CAs inhibit the T cell proliferation directly through stimulation of □-ARs and induction of cAMP in these cells (125-128). An additional CAs-induced inhibition operates through suppression of the production of IL-2, a cytokine that is an important co-stimulatory molecule in T cell proliferation (129). The proliferative response of CD8+ T cells is inhibited to a greater extent than CD4+ T

cells, presumably because CD8+ T cells have higher number of □-ARs (129). By inhibiting IL-1 production by monocytes and IL-2 and IFN-□ production by lymphocytes GCs may also contribute for decreased lymphocyte proliferation. Recently, Wheway *et al.* suggested that NPY may have a bimodal role via the Y1 receptor in the immune system, serving as a strong negative regulator on T cells as well as a key activator of APC function. According this model Y(1) expression on APCs is essential for their function as T cell priming elements. Conversely, Y(1) signaling in T cells plays a regulatory role without which T cells are hyper-responsive: NPY, signaling through Y1 on T cells inhibits T cell activation/effector differentiation but is not able to shut off the function of preexisting proliferating effector T cells (130).

Antibody Production

When B cells and Th cells are exposed to Th cell-dependent antigens, NE, through stimulation of □□ receptors, exerts an enhancing effect on B cell antibody (Ab) production (27;131). One mechanism for this enhancement may involve CAs-induced increase in the frequency of B cells differentiating into Ab-secreting cells. Moreover, Th cells not only activate B cells during cell-to-cell interaction, but they (Th2 cells) also provide the cytokines necessary for B cell growth. Thus, the □□-AR agonists salbutamol and fenoterol potentiate IL-4 induced IgE production by human PBMC, while they inhibit IFN-□ production by these cells (132). Furthermore, salbutamol induces an increase of the *ex vivo release* of IL-4, IL-6 and IL-10 (133). GCs and IL-4 have synergistic effects on the triggering and differentiation of B cells into IgE-producing plasma cells. In addition, patients with asthma, after 7-day treatment with 40 mg prednisone daily have a rise in serum IgE levels (134;135).

CONCLUSIONS AND CLINICAL IMPLICATIONS

Although interest in the Th2 response was initially directed at its protective role in helminthic infections and its pathogenic role in allergy, this response may have important regulatory functions in countering the tissue-damaging effects of macrophages and Th1 cells (5). Thus, an excessive immune response, through circulating cytokines or through stimulation of the afferent vagus, stimulates the HPA axis and the sympathetic nervous system (Figure 1). The subsequent release of cortisol and epinephrine may trigger a mechanism that inhibits, systemically, Th1 functions and pro-inflammatory cytokine production, but potentiates Th2 and anti-inflammatory responses (3;136). This appears to be complemented by locally released NE, and Ach and VIP, released by the sympathetic nerve terminals and the efferent vagus, respectively (3;88;93).

On the other hand, in certain local responses, and under certain conditions, GCs and CAs may actually boost regional innate immune responses in a transitory fashion, through induction of IL-8, IL-1 and TNF-□□production, TLR-4 expression in resting cells and short-term increase of NK cell and neutrophils numbers. This might be aimed to localize the inflammatory response, via stimulation of neutrophils accumulation and activation of macrophage activity. Importantly, during an immune response, the activation of the stress system, however, through induction of a Th2 shift, in conjunction with the increase of the ‘anti-inflammatory’ efferent vagus activity in visceral organs, may actually protect the organism from systemic “overshooting” with type 1/pro-

inflammatory cytokines and other products of activated macrophages with tissue damaging potential (see also Refs. 2;3;93;136;137). Although a complete discussion is beyond the scope of this chapter, during chronic immune or non-immune stress and/or inflammation, abnormalities in the ‘systemic anti-inflammatory feedback’ or ‘hyperactivity’ of the local pro-inflammatory factors, and particularly the CRH/SP-histamine axis, and the induction of IL-6, IL-8, CRP secretion and vasodilatation, may play a role in the pathogenesis of infections, autoimmune and atopic/allergic reactions, or obesity and atherosclerosis.

Acute or chronic stress-induced Th2 shift might specifically increase the susceptibility of the individual to intracellular infections, the defense against which is primarily through cellular immunity mechanisms – e.g., mycobacterial, *Helicobacter pylori* , HIV or common cold viral infections (11;136;138-141). Additionally, NE, directly accelerate HIV-1 replication, while the HIV-1 accessory proteins, Vpr, acts as a potent co-activator of the host glucocorticoid receptor rendering lymphoid cells hyper-responsive to GCs (142-145). Some of the instability in some inflammatory responses, such as leprosy might also be secondary to the damage of sensory C- and sympathetic nerve fibers and dysregulation of inflammation (146). A massive release of GCs, CAs, histamine and adenosine triggered by major injury (serious traumatic injury and major burns or major surgical procedures) via an induction of a Th2 shift may contribute to the severe immunosuppression and the severe infectious complications observed in these conditions (136;147-152).

Patients with RA have hypoactive HPA axis and SNS in the settings of severe chronic inflammation, characterized by increased production of IL-1, IL-6 and TNF-α. Thus, a hypoactive stress system may facilitate or sustain the Th1 shift, observed in autoimmune diseases, such as RA. An additional factor might be the preponderance of about 10:1 for primary sensory, SP positive fibers as compared with sympathetic fibers in synovial tissues of RA patients. Alternatively, stress system hyperactivity may intensify the Th2 shift and induce or facilitate flares of SLE (2;3;136;153-155). The third trimester of pregnancy and the early postpartum might represent typical example of how abrupt or substantial changes of several hormones might orchestrate autoimmune disease activity through modulation of cytokine production (54;153;156), (see Figure 5).

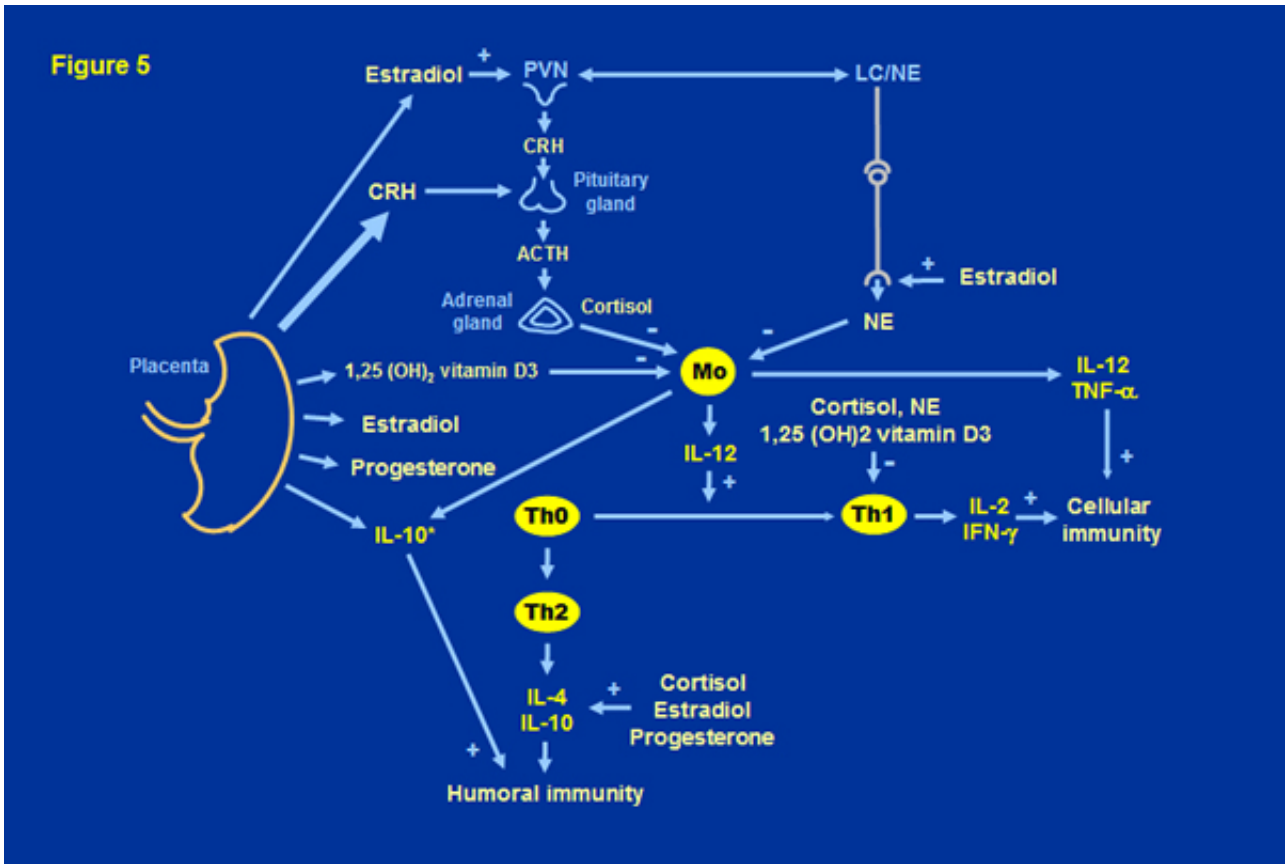

Figure 5.A proposed model of the role of different hormones in regulation of innate, and Th1 and Th2 cytokine profiles during pregnancy. Hypothalamic CRH stimulates the secretion of pituitary ACTH, which in turn triggers the secretion of cortisol from the adrenal cortex. During human pregnancy, the placenta is the major source of circulating CRH. The placenta also secretes IL-10 that may stimulate humoral and suppress cellular immunity. The sympathetic system innervates all peripheral tissues, including blood vessels and lymphoid organs. Upon activation, the sympathetic nerve terminals in these organs release NE locally and into the blood stream. Cortisol, NE, 1,25(OH)2 vitamin D3, estradiol and progesterone have multiple and divergent effects upon the immune system. *Cortisol does not affect but NE up-regulate the production of IL-10 by monocytes. Note that cortisol and estradiol up-regulate IL-10, while progesterone potentiate IL-4 production by Th2 lymphocytes. In addition, estradiol stimulates the activity of the CRH neurons, and increases local NE concentrations by blocking its uptake. Thus,in vivo,estradiol might amplify the effects of cortisol and NE. The net result of these complex hormonal effects is suppression of IL-12 and TNF□□ production by monocytes, whereas peripheral lymphocytes secrete less IFN-□ and IL-2 but more IL-4 and IL-10, particularly in the 3rd trimester. This hormonally induced Th2 shift may suppress Th1-related diseases such as RA and MS during pregnancy, while the rebound of IL-12 and TNF□□ production, and Th1 responses in the postpartum may facilitate the flares or the onset of these diseases. Note that several other factors, besides hormones (e.g. antibodies, soluble cytokine receptors, etc.) that most likely are also involved in the modulation of Th1/Th2 balance during pregnancy and postpartum, are not discussed here.Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; IL, interleukin; LC, locus ceruleus; Mo, monocyte; NE, norepinephrine; PVN, paraventricular nucleus; Th, T helper cell; TNF, tumor

necrosis factor. (From reference 54).

Allergic reactions of type 1 hypersensitivity (atopy), such as asthma, eczema, hay fever, urticaria and food allergy, are characterized by dominant Th2 responses, overproduction of histamine and a shift to IgE production. The effects of stress on atopic reactions are complex, at multiple levels and can be in either direction. Stress hormones acting at the level of APCs and lymphocytes may induce a Th2 shift, and, thus, facilitate or sustain atopic reactions, however, this can be antagonized by their effects on mast cells and alveolar macrophages (see also Refs. 136;157;158).

Low levels of IL-12 and local overproduction of IL-10 and TGF-□ have been associated with tumor growth (159;160). These data suggest that stress hormone-, histamine- and/or adenosine-induced inhibition of IL-12 and potentiation of IL-10 and TGF-β□production, and subsequent suppression of cellular immunity may contribute to the increased growth of certain tumors (80;161-165). Clearly all these hypotheses require further investigation, but the answers should provide critical insights into mechanisms underlying a variety of common human diseases.

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