Integration and Regulation of higher organisms by the neuroimmune super system

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Abstract
It is now apparent that the Nervous-Endocrine and Immune Systems (IS) form a regulatory circuitry in higher animals and in man. Further, these three systems are mutually interdependent for their function and therefore, here it is designated as the Neuroimmune Supersystem (NISS). Within NISS there is continuous communication via innervations, hormones, neurotransmitters, neuropeptides and cytokines. In the central nervous system (CNS) glia cells and also neurons are of bone marrow origin. The initial phases of lymphoid cell development are dependent on neuroendocrine factors. Later on with immunological maturation cytokines become prominent in immune regulation under homeostatic (physiological) conditions. Immunological memory cells show a fair amount of autonomy. The immune system recognizes peptide sequences (T lymphocytes) and also the three dimensional structure of antigenic molecules (e.g. B lymphocytes produce antibodies that recognize tertiary structure). This recognition will induce cytokines in immune cells, some of which have the capacity to signal the CNS/NISS either directly or via nerve signals. In the hypothalamus such signals are transmitted to the paraventricular nucleus (and to some related nuclei), which function as the centre of immunoregulation. The CNS will respond to the cytokine signals by the secretion of hormones, neuropeptides and cytokines in order to properly regulate the immune system. The CNS controls through its interaction with IS the invasion of the host by microbes and by other foreign materials as well as it defends the body against mutations and against cancer. Cytokines are newly recognised and shared mediators of the NISS.

Keywords: Neuroimmune Supersystem, integrative regulation, regulatory physiology, chemical sensation by the brain, host defense.

INTRODUCTION
The fundamental role of the CNS in maintenance of vital bodily functions is well recognized already in primitive cultures. The interaction between the hypothalamus and of the pituitary gland has been elucidated during the first half of the 20th century. These results prompted the term of Neuroendocrine system (NES), rather than CNS. These two systems interact continuously and form regulatory circuits for the numerous hormones NES is producing. The hypothalamus provides releasing factors towards the pituitary gland, which in turn regulate hormone secretion by the pituitary gland (e.g. Thryotropin Releasing Hormone – TRH, releasing thyroid stimulating hormone – TSH and Prolactin (PRL), probably also Growth Hormone (GH); Arginine Vasopressin –AVP, stimulating ACTH and PRL. Corticotropin Releasing Hormone – CRH, for the release of Adrenocorticotropic Hormone – ACTH; Gonadotrope Releasing Hormone-GNRH, for the release of Follicle Stimulating Hormone – FSH and Luteinizing Hormone- LH. More recently

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recognized factors are urocortin, which is a CRH analogue, grehlin a GH releasing factor. The releasing hormones stimulate the release of specific hormones from the pituitary gland that are involved in the regulation of growth, development and adaptive immune function (primarily GH and PRL); thyroid hormones are considered as metabolic regulators, however these hormones also affect immune and inflammatory responses; the regulation of the hypothalamus-pituitary adrenal (HPA) axis, which regulate metabolism, immune and inflammatory reactions and numerous other parameters in the body, such as glucose metabolism and blood pressure, for instance. The HPA axis plays a fundamental role in the stress response and in host defence during acute illness. The primary role of the GNRH – LH – FSH axis is the regulation of reproduction. However other functions are also obvious, such as the modulation of immune/inflammatory reactions, which may be related to the primary function (Berczi et al., 2003b; Taub, 2008; Gravanis et al. 2005; Kronenberg, 2004).

Traditionally ADIM was regarded as a self-regulated and intelligent system that has the capacity to recognize foreign microbes and foreign material in general and respond to it by antibody formation, by cell mediated immunity or by both kinds of responses. This system had the capacity to recognize self, and normally exhibited self-tolerance. Self-non-self recognition and the capacity to establish memory of immune stimulation were thought to be fundamental to normal immune function (Paul, 1999a).

NATIM is an ancient form of immunity, which comprised of diverse mechanisms. Highly preserved homologous epitopes (homotopes) are recognized by germ line coded receptors, such as natural antibodies, tall-like receptors, endotoxin binding protein, mannose binding protein, C-reactive protein and so on. Others introduced the concept of pathogen associated recognition patterns, which are recognized by cells of NATIM. This system is present at birth and it is never lost and is ready to react instantaneously against microbes or against other insults to the body. This is in contrast with ADIM, which needs 5-10 days for the primary response and 4-5 days for the secondary response (Berczi 1998; Berczi et al. 1998 a,b; Medzhitov et al., 2002; Chow 2005; Berczi, 2005; Berczi et al., 2005).

Although the HPA axis was known to play a role in the stress response and in the regulation of inflammation, since the discovery of Hans Selye (1936), the interaction of other pituitary hormones with the immune system has been discovered more recently (Nagy at al., 1978). In this article the development and current status of Neuroimmune Biology (NIB) is summarized. The significance of this newly emerging science is the demonstration that NISS coordinates host defence against infection, injury, mutations and cancer. Indeed NISS is in control of the biology of higher organisms for their entire life cycle. For recent reviews please see (Quan et al., 2007; Wrona 2006; Webster et al., 2002).

THE NEUROIMMUNE SUPERSYSTEM.

Immune derived cells and mediators are present in the CNS and are part of the neuroimmune regulatory equation. The immune cells in the CNS show enhanced activity after immunization, infection or stress (Penkowa et al. 2007; Suzumura, 2007; Kannan et al. 2007; Goehler, 2007; Korneva et al. 2007; Katafuchi, 2007;) and in various pathological conditions, such as depression, and neuro-degenerative disorders (e.g. multiple sclerosis [MS], Alzheimer’s disease, Parkinson’s disease and stroke). These conditions are associated with many elements of inflammation and autoimmunity. Cytokines and chemokines initiate and propagate the inflammatory/immune response in these pathologies. In MS there is continuous realignment and redundancy in the inflammatory and immune responses (Phelps et al. 2007; Clarkson et al. 2007; Ketlinsky et al. 2007; Dunn, 2007; Summers, 2007). Cytokines also have behavioral effects (Aubert, 2007; Neveu, 2007).

There is much more to these systems than simply sharing cytokines and other mediators. The neuroendocrine and immune systems do not only interact, but rather, these organ systems rely on each other for mutual support both in health and in disease. The thymus develops from the neural crest, which also gives rise to the CNS. Moreover, glia cells that represent roughly 50% of brain cells, are related to the monocyte-macrophage lineage and are bone marrow derived. The new and very important information is that neurons themselves differentiate from bone marrow derived stem cells (Szentivanyi et al. 2003; Gottfried-Blakemore et al. 2007; Stewart et al. 2002). Thus the brain relies on the
bone marrow for rejuvenation and healing ("plasticity"). Indeed, recent evidence indicates that inflammatory cells and cytokines exert a neuroprotective effect during traumatic brain injury (Correale et al. 2007). We know for some time that the brain shares adhesion molecules and numerous cell surface receptors with lymphocytes. It is now also clear that cell-to-cell and cell-to-matrix interactions play important roles in brain physiology and pathology (Berczi et al. 2003a; Wiranowska et al. 2007).

Until recently the Immune System has been considered as an autonomous system. Lymphocytes were known to be equipped with sophisticated receptors for the recognition of antigen and were capable of defending the host from pathogenic insults. It was also recognized that the Immune System was well organized and was regulated by internal regulatory pathways (Paul, 1999b). However, on the basis of common developmental origin, shared stem cells, receptors and mediators and mutual inter-dependence, we proposed that the nervous-, endocrine- and immune systems are integrated parts of a united Neuroimmune Supersystem. This Supersystem coordinates and regulates all the physiological and pathological processes in higher animals and man for their entire life cycle. Lymphocytes, like neurons, are sensory cells with the capacity to recognize chemical structure and to distinguish self from non-self. They store such information and are capable of memory responses. Lymphocytes are also capable of conveying information on chemical (antigenic) abnormalities in host tissues to the brain via cytokine signals. Immune cells are essential for defending the body from foreign invading pathogenic organisms as well as control mutation and eliminate aberrant cells from the host. It is now clear that immune cells are also involved in normal physiological regulation of host tissues and organs (Blalock, 1984; Berczi, 1987; Conti et al. 2007).

**IMMUNOCOMPETENCE**

*Adaptive Immunocompetence*

Growth hormone (GH), prolactin (PRL) and placental lactogen (PL) hormones represent the Growth and Lactogenic Hormone Family (GLH). These hormones regulate growth and development in utero and after birth. GH stimulates the production of insulin-like growth factor I (IGF-I) in the liver and in other tissues and organs, including the immune system. IGF-I is a peptide hormone with structural relation to insulin and with cross-reactivity at the receptor level. Insulin and IGF-I do not only bind to each other’s receptor, but also mutually regulate receptor levels, which is proportional to their ability to occupy that particular receptor. Prolactin also has the capacity to stimulate IGF-I in the liver and in other tissues, which has been named by Nicoll and co-workers as synlactin. With the discovery of IGF many investigators assumed that growth hormone action is really mediated by IGF. This view is still held by a significant proportion of investigators (Berczi et al. 2003g; Phillips et al. 1980; Blundell et al. 1980; Rosenfeld et al. 1982; Mick et al. 1985; Nicoll et al. 1985).

GH is necessary for target cell activation. One important aspect of GH action is the stimulation of IGF-I in responding cells. In turn, the locally induced IGF-I will act as an autocrine and paracrine growth factor, completing the mitogenic cycle in GH targets (Casauneva, 1992). There are other hormones/cytokines that are capable of inducing IGF-I in certain target cells. This implies that such hormones/cytokines also activate their targets similarly to that of GH, in a manner analogous to the competence-progression model of cell proliferation. Such hormones are IL-3, GM-CSF and TGFβ1 in the bone marrow and estradiol for the mammary gland (Kelley et al. 1996; Kelley et al. 1998; Fournier et al. 2001; Kveiborg et al. 2001). The tropic effect of these hormones on their specific target organs is also based on two signals.

The PRL-dependent Nb2 rat T cell lymphoma cell line responds to serum factors (IGF-I) only after being primed by PRL. Most importantly, the magnitude of the mitogenic response is directly proportional to the concentration of PRL used for priming (Berczi, et al., 1987). In vivo observations in hypophysectomised (Hypox) rats revealed that organ weight, DNA and RNA synthesis and cell proliferation in the thymus, spleen and bone marrow, and immune reactivity require the presence of pituitary GH or PRL. These experiments show that lymphocyte proliferation in primary and secondary lymphoid tissue and immunocompetence are dependent on pituitary GLH. Redundancy was also demonstrated as either PRL or GH was sufficient to restore the immune system. Placental lactogen was also capable of immune restoration (Berczi et al. 1991).
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Figure 1: Immunoconversion during the acute phase response.

The acute phase response (APR), or febrile illness is a systemic inflammatory reaction. Fever is a hallmark of the APR. Cytokines, primarily interleukin-1 (IL-1), IL-6 and tumour necrosis factor (TNF)-alpha, are released by the immune system and act directly on the brain or indirectly on nerve terminals that lead to the brain. The cytokine signals are registered in the hypothalamus and a neuroendocrine and metabolic response is initiated. From the hypothalamus corticotropin releasing hormone (CRH) and vasopressin (VP) are secreted during APR. Both of these peptides stimulate the hypothalamus-pituitary-adrenal axis (HPA). In addition VP has the capacity to stimulate prolactin (PRL) secretion. Initially CRH prevails and the activation of the HPA axis is dominant. This is coupled with "sympathetic outflow" from the adrenal gland. Glucocorticoid (GC) and catecholamine (CAT), levels are increased and together with TNF alpha are of prime importance of inducing thymus involution (e.g. by inducing apoptosis of CD8+4+ thymocytes) and of inhibiting the T cell dependent adaptive immune system. Suppressor/regulatory T lymphocytes (Tsr), which inhibit adaptive immune responses are stimulated under these conditions. Other factors that are likely to contribute to this suppression are the down-regulation of growth hormone and prolactin synthesis and zinc deficiency.

During APR the synthesis of acute phase proteins (APP) is amplified in the liver by IL-6, GC and CAT. Serum C-reactive protein (CRP) will go up as much as 1000 times of the basal level within 24-48 hrs. CRP is capable of recognizing pathogenic organisms and to activate complement and leukocytes for phagocytosis and cytotoxicity. Other serum proteins with similar biology are lipopolysaccharide-binding protein (LBP) and mannan binding protein (MBP). Additional acute phase proteins (APP) are fibrinogen and a number of anti-inflammatory and enzyme inhibitory proteins, that also rise in the serum during APR. Natural antibodies, that are poly-specific are also stimulated during APR and serve to identify pathogenic agents, which is followed by immune activation. Therefore the essence of febrile illness is to switch over the immune system from the adaptive (T cell dependent) mode of reactivity to the activation of innate/natural immune mechanisms. This process is coined as immunoconversion.

During the chronic phase of inflammatory disease CRH will subside and VP will take over the regulation of the HPA axis. Because VP also stimulates PRL secretion, it is hypothesized that VP alters the neuroendocrine milieu to favour the restoration of adaptive immunocompetence. This process is named immunoreversion, which will lead to recovery from acute illness.

It is apparent from APR that the immune system signals the brain about foreign substances and about altered self antigens, and the brain responds by hormone release, via nerve discharge (e.g. sympathetic outflow), metabolically and by the mobilization of the important organs (brain, bone marrow, liver, leukocytes etc.), all in the interest of host defense. Cytokines play a fundamental role in this Neuroimmune Host Defense reaction, which represents an emergency response for survival. Through this mechanism the brain senses chemical changes within the body and mounts a rapid and effective defense reaction against the invader/insult.
Like GH, PRL is also a pleiotropic hormone with multiple targets. On the basis that GH is able to cause the proportional growth of the entire organism one may conclude that the entire body is a target for GH. PRL seems to affect most tissues except to stimulate body growth, though a limited growth promotion is present. Pituitary GLH induces IGF-I within the immune system as observed by several investigators. Both GH and PRL were capable of inducing IGF-I within the thymus and spleen of Hypox rats. This furnishes additional evidence for the ability of these hormones as growth promoters of the immune system (Berczi et al. 2003b; Kelly et al. 1991, Nagy et al. 1989, Nagy et al. 1992).

GLH are essential for the maintenance of vital bodily functions (Sinha et al. 1982; Nagy et al. 1992). In mammals the fetus is exposed to high levels of placental GLH as these hormones are present in the amniotic fluid in high concentrations (Hill, 1992). During embryonic life placental GLH play a fundamental role in the growth and development of the foetus and of the immune system and pituitary hormones are not required as fetuses with the congenital lack of the pituitary gland develop normally in utero (Potter et al. 1975). During postnatal life the pituitary gland assumes the role of growth control in the organism (Glasscock et al. 1990). Bone marrow and thymus function and the maintenance of immunocompetence during postnatal life depend entirely on pituitary GLH (Berczi et al. 2003b). On this basis it has been proposed that GH and PRL are the hormones of adaptive immunocompetence (Berczi et al. 1987; Berczi, 1994).

**Innate or Natural Immunocompetence**

Higher animals and man are born with this innate immune system and never loose it. The cells of the NATIM (e.g. natural killer cells, gamma-delta T lymphocytes, CD5+ B lymphocytes, monocyte-macrophages, granulocytes, etc.) have genetically determined (germline coded) receptors for highly preserved homologous epitopes (homotopes) that are present in pathogenic microbes in injured/degenerated cells and also in cancer cells (Berczi, 1998; Chow 2005). Some examples of homotopes are bacterial LPS, mannoside residues in infectious agents, pathogen associated recognition patterns in numerous pathogenic microbes (Medzhitov et al. 2002) and cancer antigens. NK cells kill targets that express tumour antigens and lack MHC antigens. Because natural immune cells are capable of responding instantaneously to the antigen they recognize, they provide the first line of defence for the host. However, in acute illness natural immune mechanisms are amplified so the host organism relies on this system during the final struggle for survival. Because NATIM is hard wired for response to the antigen, little, if any, regulation can take place at this level. Therefore, NATIM is regulated by cytokines, hormones, neurotransmitters and neuropeptides (Berczi et al., 1998; Berczi, 2005; Berczi et al., 2005).

**GROWTH SIGNALING IN THE IMMUNE SYSTEM**

**Signalling by GLH**

As already pointed out, we consider GLH as the first (competence) signal for lymphocyte proliferation. These hormones stimulate the production of mature T and B lymphocytes, which are required for the initiation of an immune response. Next, antigen presenting cells (APC) interact with helper T cells and later on the helper T cells with B cells (antibody response) or immature antigen sensitive T cells (cell-mediated immunity). This adherence interaction stimulates the secretion of cytokines from helper T lymphocytes, which function as paracrine growth factors. The antigen signal is modified by additional “co-stimulatory” and inhibitory signals, which are also delivered by adhesion molecules (Berczi I, et al. 1991; Berczi et al. 2003f,g).

Cytokine signals complete the mitogenic stimulus and enable the immature cell to proliferate (clonal expansion). Multiple cytokines are available to deliver this signal, which varies according to the type and stage of the immune response [Paul, 1999b, Berczi et al. 2003f; 2003g). It is known that lymphocytes are capable of producing GLH, however the exact function of these hormones in immune reactions have not been elucidated in detail.

GLH show redundancy in the maintenance of immunocompetence. Current evidence also indicates that IGF-I may be substituted for in the immune system by IGF-II or insulin. Clearly, immune function, as many other functions in the body are maintained by multiple hormones and cytokines that show overlap and redundancy (Berczi et al. 2003b, Dorshkind et al. 2000).
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Human GH and other primate GH are known to act on the PRL receptors and to exert lactogenic activity in many species, which indicates functional overlap within GLH hormones. The major signal transduction pathway, which involves the Janus kinase (JAK) and signal transducers and activators of transcription (STAT) nuclear regulatory factors, is shared between cytokines and growth and lactogenic hormones. STAT knockout mice show severe developmental and immune deficiencies (Freeman et al., 2000). This may signal functional overlap between the immunoregulatory function of GLH and of the cytokines that use the JAK/STAT signaling pathway. This remains to be investigated.

**Antigen Presentation**

Adaptive immune reactions are mediated by lymphocyte clones that have specific receptors for the determinants (epitopes) of the antigen. Initially, the antigen was assumed to be the sole signal that instructed immunocytes to make antibodies by some sort of recognizing and copying mechanism (Silverstein, 1999). Later it was realized that antibody specificity is genetically coded and that the antigen has to be digested and presented by specialized antigen presenting cells (APC) to T lymphocytes. Phagocytic mononuclear cells (monocyte-macrophages), B lymphocytes and some specialized cells (e.g., dendritic cells, Langerhans cells, Kupffer cells) are “professional” APC that present antigen via major histocompatibility (MHC)-I and MHC-II. In the central nervous system the macrophage-related microglia and to a lesser extent, astrocytes, are involved in antigen presentation as well as in inflammatory responses. However, all nucleated cells are capable of antigen presentation by MHC-I, which is constitutively expressed by such cells. In addition, IFN is capable of inducing the expression of MHC-II in somatic cells, which enables them to present antigens by this pathway. Major histocompatibility antigens bind peptides during their intracellular biosynthesis and carry them to the surface of APC. In turn the digested (processed) antigenic peptide-MHC complexes are recognized by T cells as “altered self” (Germain, 1999; Cresswell, 1994; York et al. 1996; Aloisi, 2001; Gebicke-Haerter, 2001).

The T cell receptor recognizes sequentially (linear recognition) the target peptide. The MHC self peptide complex is recognized as “self” and a complex with foreign peptide as “non-self” in this process. This self-non-self recognition has evolved to provide protection against autoimmune reactions while foreign invaders are attacked. The requirement for T cells to recognize antigens in the context of MHC assures that infected and cancerous cells are specifically eliminated by killer cells. However, soluble antigen, which is not processed and not associated with MHC antigens, is not capable of triggering killer T lymphocytes. This mechanism prevents the exhaustion of T cells by viremia or by other antigen that is present in the circulation (Germain, 1999). The immunoglobulin B cell antigen receptor is capable of recognition of the tertiary structure of native molecules even microorganisms (conformational recognition). B cells engulf the antigen they recognize, digest (process) them and present peptides from the antigen to helper T lymphocytes via their surface MHC antigens. Such helper cells adhere to the B cells and are activated for cytokine production (IL 4, 6 etc,) which will promote B cell proliferation and maturation to antibody producing (plasma cells) (Germain, 1999; Berczi et al., 2003f).

**IMMUNE NEUROENDOCRINE FEEDBACK SIGNALS**

Interleukin -1 (L-1) was the first cytokine shown to stimulate the hypothalamus-pituitary-adrenal (HPA) axis (Besedovsky et al. 1981; Besedovsky et al. 1987; Sapolsky et al. 1987). Purified natural and recombinant human forms of IL-1 can stimulate adrenocorticotropic hormone (ACTH) and corticosterone output in mice and rats. Later, TNF\∀, different types of interferons, IL-2, IL-6, IL-11, IL-12, leukemia inhibitory factor (LIF), GM-CSF, oncostatin, and stem cell factor (SCF) were found to affect the HPA axis and the release of other pituitary hormones (Bernton et al. 1987; McCann et al. 1994; Besedovsky et al. 2007.)

Cytokines are known to affect brain function directly, affect endocrine glands as well and act on peripheral nerves such as the vagus and sensory nerve fibers, which in turn transmit their signals to the hypothalamus. Eventually all forms of neural signaling to the brain acts on the hypothalamus, on the paraventricular nucleus in
particular and also the supraoptic nucleus, which affect pituitary function, including the HPA axis and of GLH hormones. The brain may release immunostimulatory/prinflammatory signals (e.g. GH, PRL) and immunosuppressive/anti-inflammatory signals by HPA activation towards the adaptive immune system (Berczi et al. 2003i; Besedovsky et al. 2007; Conti et al. 2007). Catecholamines regulate cyclic AMP, GMP and calcium influx. A number of other mediators, including opioid peptides, act through G-protein linked adenylate cyclase receptors as well. Because Ca^{2+} is needed for cellular activation and phosphorylation, which are fundamental mechanisms of signal transduction by membrane bound receptors, these mediators are designated as *signal modulators* in immune activation and in cellular activation in general. Catecholamines may play immunostimulatory (alpha-adrenergic) and immunosuppressive (beta adrenergic) roles, whereas acetylcholine is considered to be immunostimulatory. Substance P and calcitonin gene related peptide are pro-inflammatory and somatostatin are anti-inflammatory neuropeptides (Berczi et al. 2003c,i).

The steroid hormones that play major roles in the neuroimmune regulatory network include glucocorticoids, aldosterone, estrogens, androgens and vitamin D. These hormones have cytoplasmic or nuclear receptors, which are transcription factors that directly regulate gene expression. Glucocorticoids are produced in the adrenal gland and are fundamental to immune function. Physiological levels are required for the normal development and functioning of the immune system. Under pathophysiological conditions the serum level of glucocorticoids is elevated, which plays an important role in the suppression of the adaptive immune response that depends on T lymphocytes. Glucocorticoids also exert a powerful anti-inflammatory effect. Elevated glucocorticoids during acute phase reactions augment natural immunity, the production of natural antibodies and support the production of acute phase proteins by the liver (Berczi et al. 2003e).

Luteinizing hormone releasing hormone and gonadotropins exert a direct regulatory influence on the immune system, in addition to the regulation of sex steroid hormones. In turn immune-derived cytokines regulate the production of gonadotropins. These mechanisms insure the coordination of reproduction with health status and prevent inopportune conception (Berczi et al. 2003e).

Estrogens regulate the thymus and suppress cell-mediated immune reactions. The antibody response and natural immunity (NK cytotoxicity, phagocytosis) are augmented by estradiol. Testosterone is immunosuppressive during trauma and shock. Many of the immunological effects of testosterone are due to its conversion to estradiol by aromatase in the thymus and in other lymphoid organs. The adrenal androgen, dehydroepiandrosterone stimulates immune reactions in experimental animals and in man. It antagonizes the immunosuppressive effect of glucocorticoids and its age-related decline may contribute to the immunodeficiency that develops in elderly individuals. Progesterone is a powerful immunosuppressive hormone. It plays a major role in the protection of the foetus during mammalian reproduction. Progesterone also contributes to the generation of self tolerance and protects against the excessive activation of the immune system (Berczi et al. 2003e).

1,25-dihydroxy vitamin D3 (VD3) is a major immunoregulator with a powerful immunosuppressive potential. Deficiency of VD3 plays an important role in the development of autoimmune disease. VD3 is also required for normal immune function and for proper defence against infectious disease and cancer (Berczi et al. 2003e).

**HOMEOSTASIS: THE IMMUNE-NEUROENDOCRINE CIRCUITRY**

Under physiological conditions the *immune system* provides continuous defense against infectious agents, injury, harmful mutations and cancer, and it is part of the homeostatic neuroimmune regulatory circuit that co-ordinates the normal function of the entire organism. The immune system provides local and mobile defense and regulation and it has enormous capacity to deliver defense and regulatory molecules to sites that are in need. Every organ and tissue possesses stromal lymphoid elements that intervene locally to control autoimmune reactions, inflammation, and in general, participate in the physiological processes (Berczi et al. 2003j).

*Adaptive* cell mediated and humoral immunity and immunological memory are reactions
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exerted by T and B lymphocytes in concert with members of the leukocyte series. *Innate* host defense relies on non-immune mechanisms, on specialized immune cells, such as natural killer cells, (T lymphocytes and CD5⁺ B cells. The complement system and of T and B lymphocytes activated by alternate pathways are also part of the natural immune system. The natural immune system relies on germ-line coded receptors that recognizes evolutionarily highly preserved homologous epitopes (homotopes) on microbes and also on self components (Paul, 1999a; Berczi *et al.* 2005).

Cell-to-cell interactions by the antigen receptor and of MHC molecules and by other adhesion molecules are fundamental to immune activation as well as to stromal regulation. Cytokines are an essential part of this regulatory system. In addition, the immune system interacts with the neural elements and mediators, parenchymal and stromal cells as part of the local neuroimmune circuits that govern the organ/tissue under physiological circumstances (Berczi *et al.* 2003f).

**Immunoregulation by the HPA axis.**

*Glucocorticoid hormones* exert a multitude of functions that affect virtually every cell in the body. The physiological significance of glucocorticoids is most remarkable at times of stress, when the hypothalamic-pituitary-adrenal axis (HPA) is fully mobilized. The same hypothalamic hormone that stimulates the HPA axis, CRF also mediates behavioral, autonomic and neuroendocrine responses to stress in rodents and primates. Hyperfunction of CRF neurons, therefore, appears to underlie a variety of psychiatric, gastrointestinal, cardiovascular, metabolic and reproductive illnesses attributable to stress (Besedovsky *et al.* 2007).

**ACUTE ILLNESS**

**Neurogenic inflammation.**

The release of neuropeptides, including tachykinins and calcitonin gene-related peptide, from sensory nerves via an axon or local reflex may exert an inflammatory effects in the airways. This neurogenic inflammation may be initiated by sensory nerves, which are activated by inflammatory mediators and irritants. The phenomenon of neurogenic inflammation is well known in rodents and contribute to the inflammatory response to allergens, infections and irritants in animal models. However, the role of neurogenic inflammation in airway inflammatory diseases, such as asthma and chronic obstructive pulmonary disease is still uncertain. There is still little direct evidence for the involvement of sensory neuropeptides in human airways. Initial clinical studies designed to block neurogenic inflammation have not been encouraging. Therefore, it is necessary to perform prolonged studies of severe forms of airway disease in the future to explore the role of neurogenic inflammation (Jancso, 1960; Barnes, 2003).

**Defensins (DEF)**

Defensins are antimicrobial cationic peptides with a cysteine-stabilized amphipathic structure. Defensins are normally localized in phagocytes (neutrophil, monocyte/macrophage) and in the epithelial cells of mucous membranes and skin. Some DEF are released into the blood during the course of infection, inflammation or stress. DEF function not only as endogenous animal antibiotic molecules, killing microbial cells and enveloped viruses, but also as physiological regulators. Defensins are implicated in the regulation of endocytosis, chemotaxis, mast cell degranulation and inflammation. Moreover, these molecules are modulators of hemostasis and neuroendocrine-immune interaction. Defensins lower the stress-induced elevation of corticosteroid levels in the blood, and abolish the stress-induced inhibition of the humoral immune response. These facts support the hypothesis that DEF are antibacterial peptides with a broad spectrum of biological activity (Korneva *et al.* 2003).

**The acute phase response**

Mild infection or sublethal dose of endotoxin elicits a brief elevation of GH and PRL in the serum, which are proinflammatory and immunostimulatory. In severe trauma, sepsis and shock, GH and PRL are suppressed, whereas glucocorticoids and catecholamines are elevated. Under these conditions an acute phase response (APR) is initiated by immune-derived cytokines, primarily IL-1, IL-6, TNFα. These cytokines elicit a profound neuroendocrine and metabolic response. Fever and catabolism prevails, and the
synthesis of acute phase proteins (APP) in the liver, cell proliferation in the bone marrow, and protein synthesis by leukocytes are elevated. This is an emergency reaction to save the organism after the failure of the adaptive immune system to protect the host. During sepsis and endotoxin shock the activation of the complement system and the release of leukocyte-derived enzymes, tissue-derived brake-down products and highly toxic cytokines seriously threaten survival. The hypothalamus-pituitary-adrenal axis is activated. Glucocorticoids play a major role in the regulation of proinflammatory cytokine production and potentiate the secretion of acute phase proteins. Some APP, such as C reactive protein, LPS binding protein and mannos binding protein in the serum are designed to combine with micro organisms and trigger their destruction by the activation of complement system and of phagocytes. The increased production of some complement components also helps host resistance. The rise in serum fibrinogen promotes blood clotting. A number of enzyme inhibitors are produced as APP, which are likely to serve to curb the non-specific damage inflicted by enzymes. Catecholamines are also elevated, which serve to inhibit inflammatory responses and to promote, even initiate, the acute phase response. Serum leptin is also increased, which governs energy metabolism as well as it has an immunostimulatory effect. If the acute phase reaction fails to protect the host, shock will develop. Patients with subclinical adrenal insufficiency succumb to septic shock almost invariably if glucocorticoid therapy is not given. However, glucocorticoid treatment of septic patients with normal adrenal function has not been helpful (Berczi, 1993;1998; Berczi et al. 1994; 1998; 2001; 2003; 2005; 2006; Haeryfar et al. 2001).

During the acute phase response the T-cell regulated adaptive immune response is switched off and natural immune mechanisms are amplified several hundred to a thousand times within 24-48 hours. This phenomenon has been designated as immunoconversion, which is initiated by immune derived cytokines, and involves profound neuroendocrine and metabolic changes, all in the interest of host defense. Therefore, natural immunity is essential for a first and last line of defense and the neuroendocrine system is an important promoter and regulator of this fundamental form of immune defense (Berczi et al. 2005; Berczi et al. 2006).

HEALING

Most people develop febrile illness on numerous occasions during a lifetime. These febrile episodes normally subside and are followed by healing and return to health and to normal adaptive immunocompetence. By now we understand how the APR develops and what it is doing. However, we know little about the recovery phase. One would expect that in accord with the tight neuroendocrine regulation of APR the recovery phase also would be regulated by neuroendocrine mechanisms. Some recent observations on the role of vasopressin in immune function and in APR appears to provide indications of the mechanism of recovery, termed as immunoreversion (Berczi et al. 2006).

Vasopressin in chronic inflammation and stress

In Sprague-Dawley (SD), and Piebald-Viral-Glaxo (PVG) rats VP but not CRF mRNA was increased in the medial parvocellular division of the hypothalamic paraventricular nucleus (PVN) in response to adjuvant arthritis (AA). The ACTH response of pituitaries of arthritic PVG rats to CRF or the combination of CRF and VP was significantly higher compared with the controls, although the ACTH response of arthritic SD rat pituitaries was unchanged (Chowdrey et al. 1995). During chronic inflammatory conditions, such as adjuvant-induced arthritis of rats, CRF does not act as the major ACTH-releasing factor. This is also true for experimental allergic encephalomyelitis, eosinophilia myalgia syndrome, systemic lupus erythematosus, and leishmaniasis. During chronic inflammation arginine vasopressin takes over as the major regulator of the HPA axis (Harbuz et al. 2003).

Chronic intermittent exposure to immobilization, insulin-induced hypoglycemia or psychological stress stimuli have been shown to increase the number of CRF cells containing VP and to increase the ratio of VP to CRF within the zona externa of the median eminence (DeGoeij et al. 1991; 1992a; 1992b; 1992c) In chronically restrained rats exogenous VP but not CRF was found to increase plasma levels of both ACTH and corticosterone (Hashimoto et al.
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1988). Chronic inflammatory stress is associated with much larger stimulation of VP than other stress models. Activation of CRH does not appear to play a role under these conditions. However, only CRH can stimulate POMC transcription, not VP (Levin et al. 1989). VP has been less potent than CRF in producing ACTH release from rat pituitaries. The effect of VP on CRF mediated ACTH release is either synergistic or additive (Antoni, 1986; Gilles et al. 1982).

Mechanisms of action of VP in APR

VP attenuated significantly the febrile response of rabbits to bacterial pyrogen. As the body temperature rose in response to the pyrogen, the level of VP in the perfusate collected from the septal area decreased (Malkinson et al. 1987).

Endotoxin may stimulate endogenous pathways that lead to the generation of NO, which in turn inhibits CRH. In addition, it generates CO, which modulates the release of vasopressin. These gases are thus potential counter-regulatory controls to the activation of the HPA (Kostoglou-Athanassiou et al. 1998).

Inhibitors of phenylethanolamine-N-methyltransferase (PNMT), which are active either peripherally (SKF 29661) or both peripherally and centrally (SKF 64139), thus lowering epinephrine (EPI) synthesis, were studied. In adult male rats SKF 64139 pretreatment significantly (p < 0.05) enhanced basal medial basal hypothalamus (MBH) and basal median eminence VP contents. LPS administration significantly (p < 0.05) decreased MBH VP in CTRL and SKF-29661-pretreated rats and diminished (p < 0.05 vs. basal values) ME VP in all groups (Giovambattista et al. 2000).

In rats 3-4 hours following LPS injection (100 micrograms/kg, i.v.), CRH gene transcription was upregulated in the PVN. Transcripts of CRH receptors type A were present in the hypothalamus 6 h after endotoxin treatment. However, no alterations in cytoplasmic VP mRNA levels were noted in rats injected with LPS. Because the dose of LPS we used stimulates ACTH secretion within 30 min, our results suggest that systemic LPS acts first within the median eminence, where it stimulates peptidic nerve terminals (Lee et al. 1995).

In alert, normally behaving ewes endotoxin potently stimulated CRH and VP secretion into portal blood of the pituitary gland, and cortisol and progesterone into peripheral blood. Both CRH and VP generally rose and fell simultaneously, although the peak of the VP response was approximately 10-fold greater than that of CRH. This stimulation coincided with significant suppression of GnRH and LH pulsatile secretion in these same ewes and with the generation of fever (Battaglia et al. 1998).
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In Holstein steers LPS increased body temperature, plasma ACTH and cortisol (p < 0.05). Abundance of anterior pituitary VP receptor V3 mRNA was decreased at 2, 4, and 12 h following LPS administration (p < 0.05) and returned to basal by 24 h. (Qahwash et al. 2002).

Regulation of the pituitary hormones by vasopressin

The ACTH response to exogenous administration of VP was impaired in V1bR-/- mice, while CRH-stimulated ACTH release in V1bR-/- mice was not significantly different from that in the V1bR+/+ mice. VP-induced ACTH release from primary cultured pituitary cells in V1bR-/- mice was also blunted. The increase in ACTH after a forced swim stress was significantly suppressed in V1bR-/- mice (Tanoue et al. 2004).

In conscious male rats icv infusion of histamine (HA) induced PRL secretion was inhibited by pretreatment with a specific antiserum to VP. A VP antagonist also inhibited the PRL response to HA and inhibited the PRL response to restraint stress. In contrast, pretreatment with a specific oxytocin (OT) antagonist had no effect on the HA- or stress-induced PRL release (Kjaer et al., 1992). Vasopressin antiserum (VP-Ab) was administered iv to lactating rats 15 min before permitting their previously isolated pups to suckle or to continuously suckled rats. The suckling-induced rise in plasma PRL levels was significantly less in VP-Ab-treated mothers when compared to rats receiving a similar amount of normal rabbit serum (Nagy et al., 1991).

Anterior pituitary cells derived from juvenile female turkeys were incubated with posterior pituitary extracts or test substances for 3 hr. Posterior pituitary extracts contained a potent substance(s) which stimulated PRL release in a concentration-dependent manner. Antisera to VP and vasoactive intestinal peptide (VIP) (1:500) completely abolished the PRL-releasing activities of their respective peptides but partially reduced (P < 0.05) the PRF activity of the posterior pituitary (el Halawani et al. 1992).

CRH or VP released ACTH and immunoreative beta-endorphin (beta-ENDir) in response to histamine and restraint stress. Pretreatment with CRH antiserum abolished the ACTH response to stress and inhibited the beta-ENDir response by 60%. Immunoneutralization with VP antiserum had only half the inhibitory effect of that seen with CRH antiserum. CRH (100 pmol i.v.) increased the plasma levels of ACTH and beta-ENDir. This effect was abolished by pretreatment with CRH antiserum, whereas pretreatment with VP antiserum prevented the CRH-induced ACTH release and inhibited the beta-ENDir response by 50%. VP (24-800 pmol i.v.) stimulated ACTH and beta-ENDir in a dose-dependent manner. CRH and VP antisera each prevented the effect of VP (800 pmol) on ACTH secretion, whereas the beta-ENDir response to VP was only inhibited by about 60% by the antisera (Kjaer et al. 1992).

Endogenous oxytocin play a role in the control of basal GH release probably by stimulating somatostatin secretion and/or inhibiting GH-releasing hormone secretion or by both actions. Endogenous VP and oxytocin play a physiologically significant stimulatory role in the control of basal ACTH release (Franci et al., 1993). The novel high-affinity non-peptide CRH 1 receptor antagonist R121919 significantly inhibits stress-induced corticotropin release and displays anxiolytic effects in rats selectively bred for high anxiety-related behavior. R121919 attenuates the stress-induced release of corticosterone, prolactin, and oxytocin. Moreover, the decrease in plasma testosterone following exposure to stress is abolished by R121919. Our data indicate that antagonism of CRH 1 receptors may prevent stress-associated endocrine alterations (Keck et al. 2003).

In rats with paraventricular nucleus lesions LPS was able to activate the hypophysial-adrenal system in the absence of hypophysiotrophic neuropeptides of paraventricular origin (Elenkov et al.1992).

This survey indicates that VP participates in immunoregulation, both by regulating pituitary hormones and by direct effect on immunocytes. It seems certain that VP is required for the maintenance of adaptive immunocompetence. Growth and lactogenic hormones are responsible for the maintenance of thymus function and of the T cell regulated adaptive immune system in a competent state. It is clear that VP has the capacity to stimulate both the HPA axis and PRL in a balanced fashion. This is in contrast with CRH, which stimulates the HPA axis only. In
APR CRH is dominant because of its resistance to GC inhibition, whereas VP is in the background. However, as it has been established, during chronic inflammatory disease VP will take over the regulation of the HPA axis. Moreover, VP has the capacity to stimulate PRL synthesis, which is suppressed during APR. PRL is an important immunostimulant, and restores adaptive immunocompetence, which sets the stage for recovery and healing. Additional studies are required to support this hypothesis.

**CONCLUSIONS: THE BIOLOGICAL SIGNIFICANCE OF NISS**

The Immune System protects against infection, injury, cancer, and mutations (e.g altered self) by self recognition and self preservation through host defense. Moreover cytokines, which are shared by the immune system and by the CNS, are required for the normal function of the CNS, ENS, IMS and in all probability, for other organs and tissues. At this point it is clear that the immune system signals the CNS about infection, injury, mutation (altered self) and cancer by cytokine signals sent directly to the CNS and indirectly via sensory nerves and the vagus nerve. The CNS responds by nerve impulses, hormone and cytokine secretion, which are aimed at resolving the problem. Phagocytosis, neutralization by antibodies, cytotoxicity by antibody-complement and by killer cells, and an inflammatory response where defense molecules and effector cells are concentrated and exert complex interactions in the interest of host defense and of healing.

It is now known that inflammatory T cells do not only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type) but these cells may only function as effector cells (e.g. Killer, or delayed hypersensitive type)

It is quite conceivable that the *neuroendocrine milieu* plays a decisive role what the outcome would be of a local inflammatory response. Thus in a CRH dominated *pro-inflammatory milieu* the destructive force of inflammation would be promoted systemically in order to eliminate the pathogen that caused the inflammatory response. However, later on VP would take over as a principal hypothalamic regulator and it is proposed to stimulate both the HPA axis and also GLH in a balanced fashion. This would result in the restoration of physiological (homeostatic) neuroendocrine milieu, which can lead to healing and recovery. It is quite likely that the occurrence of healing by T lymphocytes is stimulated by the homeostatic milieu, which has emerged in response to the elevated VP levels.

Ultimately the evidence reviewed above demonstrates that the CNS has the capacity to sense foreign (infectious agents and other foreign compounds) materials as well as altered self (mutations, cancer) by interacting with the immune system and that it is capable of directing and integrating the forces of host defense against these pathogenic situations. Here we witness an entirely new way of sensation by the CNS, which is mediated by cytokines. The response to this sensation is mediated by hormones, neurotransmitters, neuropeptides and cytokines. Cytokines are novel mediators that have been recognized recently to play an important role in the immune and nervous systems and also play an essential role in communication between the two systems.

**References:**


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