

## Neuroimmune Regulation in Health: Acute Febrile Illness and Healing

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### Abstract

Adaptive Immunity (ADIM) is maintained by Growth hormone (GH), Prolactin (PRL), and during fetal life Placental lactones (PL) fulfill this role. Vasopressin (VP) is also an ADIM regulator. ADIM is also regulated by antigens and by cytokines and chemokines. Innate immunity (INIM) is the second part of our Immune System. This system is with us for life, capable of responding instantaneously and it is with us in acute febrile illness and in other pathological situations. It protects us till the last second of life. The Hypothalamic-Pituitary –Adrenal (HPA) axis and catecholamine's regulate INIM. The acute phase response (APR), or acute febrile illness, is an emergency defence reaction against infectious disease and towards other pathogens. Here the ADIM system is suppressed and INIM function is significantly amplified. Cytokines, IL-1 beta, Tumor necrosis factor (TNF)-alpha and IL-6 stimulate corticotrophin releasing hormone (CRH), VP secretion and cause "sympathetic outflow". Colony stimulating factors activate leukocytes. CRH is a powerful activator of the HPA-axis, and elevates glucocorticoid (GC) levels. Cytokines, GC and catecholamine's (CAT) play fundamental role of INIM amplification. VP supports the APR at this stage, however when the disease turns to chronic, it is VP that will regulate, and not CRH, the chronic disease and proceed to recovery and healing. VP is able to cause recovery as it stimulates the HPA axis and also Prolactin. The ACTH-adrenal axis stimulates NATIM and suppressor regulatory (T sr), which suppresses ADIM. It is concluded that VP regulates healing and recovery from disease.

**Keywords:** Adaptive immunity; Vasopressin; Neuroimmune regulation; Glucocorticoid

### Introduction

Growth and lactogenic hormones (GLH), e.g. growth hormone (GH), prolactin (PRL) and placental lactogens (PL) are important immunoregulators. Several reviews are available on the subject [1-4]. Recent findings are that B cell differentiation into antibody forming cells is regulated by estradiol (for innate -) and by prolactin (for adaptive immune) B cells [5].

The immune system functions as natural immunity (NATIM), synonym innate immunity (INIM). We are born with this immune system and never lose it. Monocyte-macrophages, granulocytes, a subset of B cells producing natural antibodies, Natural killer (NK), T cells, gamma-delta T cells and cells of the "reticulo - endothelial system" (RES) play major roles in INIM. Innate immune cells are fully mature and are capable of instantaneous responses. Such cells also work under catabolic conditions [6,7].

The adaptive or acquired immune response (ADIM) is based on cell proliferation and maturation, thymus derived T cells mediate cellular immunity and bone marrow derived B-cells form antibodies. Mature antigen specific cells enter the blood stream. Recirculate and populate the secondary lymphoid organs, which are the spleen, lymph nodes, and mucosal lymphoid tissue [8].

In Adaptive Immune Cell growth requires anabolic conditions and time is necessary to develop from a few cell clones a whole army of immune cells. So the primary immune response takes 7-10 days, the secondary response is 3-5 days. The ADIM system is regulated by

antigen and regulatory T cells which may act by regulatory contact or by cytokines [9].

We distinguish cell mediated and humoral immunity in the ADIM system. Humoral immunity consists of antibodies, serum complement and acute phase proteins. Thymus derived, T cells may be effector (T-E e.g. Helper, killer) (gamma-delta T, and NK-T). The adaptive immune system is regulated by suppressor regulatory T cells (Tsr) and antigen, innate immunity is regulated independently of regulatory T cells [6,9].

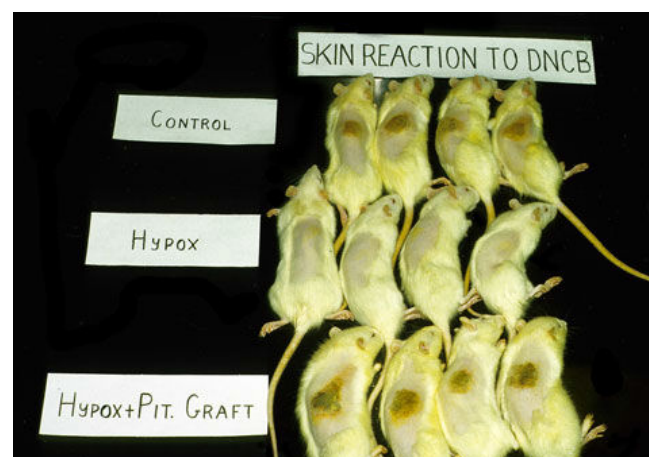


Figure 1: Skin reaction to dinitrochlorobenzene (DNCB).

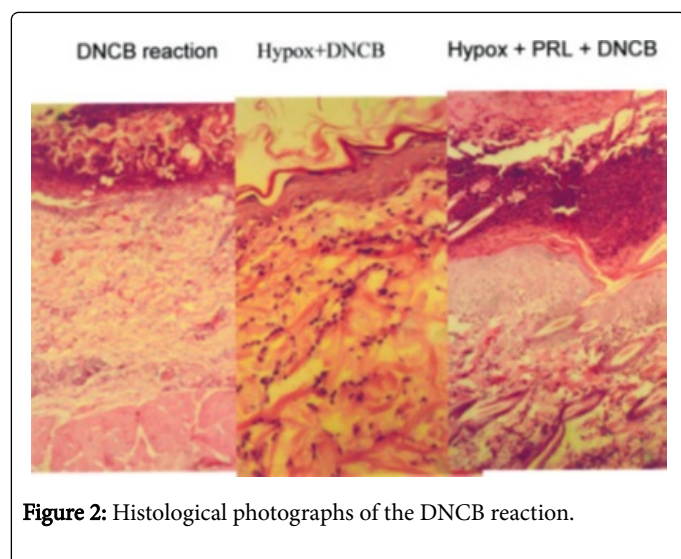
All the systems are regulated by cytokines, hormones, neurotransmitters and neuropeptides. The hypothalamus is the ultimate immunoregulator (Figure 1).

Normal control animals responded with skin inflammation 5 days after skin painting with DNCB. Hypophysectomized (Hypox) animals did not respond to DNCB challenge. Syngeneic pituitary grafts transplanted under the kidney capsule fully restored immune reactivity of Hypox rats. Note: Unlike in other species, which need to be sensitized first in order to react to DNCB, rats show natural immunity to DNCB, so they react to the first challenge.

### Hormonal Regulation of Immunocompetence

We discovered immunoregulation by the pituitary gland in 1978 [10]. Cell mediated immunity to dinitrchlorobenzene was pituitary dependent. Antibody responses were also depended on pituitary hormones. The secondary antibody response was only partially dependent on pituitary function. The rejection of skin grafts and the development of adjuvant arthritis were also depended on growth and lactogenic hormones [11]. The dopamine antagonist, bromocriptine (BRC), which inhibits pituitary hormone secretion, was as effective in immunosuppression as were hypophysectomized (Hypox) rats [12]. Adrenocorticotrophic hormone (ACTH) and glucocorticoids (GC) antagonized the restoration of adaptive immune function by GLH in Hypox rats. (Figure 1) [13,14]. GLH regulates bone marrow function [15].

Passive cutaneous hypersensitivity was not affected by Hypox (unpublished). Experimental allergic encephalomyelitis (EAE) could not be induced 10 days after Hypox, but after 21 days the animals responded with EAE [16]. Hypox rats restore their PRL levels (up to 50% by day 63) thus become immunocompetent (Figure 2).



**Figure 2:** Histological photographs of the DNCB reaction.

Treatment of Hypox rats with prolactin (PRL) restores immunocompetence. Normal animals react with mononuclear cell infiltration of the challenge site; Hypox animals have no such infiltration. In Hypox animals are treated with PRL, the inflammatory response is fully restored.

Cell growth and DNA, RNA synthesis in the thymus spleen and bone marrow are dependent on GLH. Nucleic acid synthesis in lymphoid tissue showed a direct correlation with immunocompetence.

Other experiments showed that the magnitude of tumor necrosis factor (TNF) response to bacterial lipopolysaccharide (LPS) endotoxin was controlled by the HPA axis. In adrenalectomized (ADR-X) mice TNF levels rose 60 times over normal control levels within 30 minutes of lethal LPS injection. The lethal dose was reduced 500 times in (ADR-X) mice. Treatment with dexamethasone normalised ADR-X mice [17,18].

Mice with knockout genes for prolactin or its receptor are immunocompetent [19-22]. This could be expected as such mice do have GH which can maintain immune function [19-22].

### The Regulation of Adaptive Immunity by Regulatory/ suppressor T (Tsr) Cells

During our original studies replacement doses of GLH stimulated and similar doses of ACTH suppressed adaptive immunity in Hypoxed rats. These hormones were designated as immunoregulatory.

Other hormones (e.g. steroid, thyroid hormones) were classified as immunomodulatory hormones. Initially it was assumed that the HPA axis suppresses the thymus and T cell function via GC-induced apoptosis. However, the idea of having suppressor cells was much more compelling than having hormones as immunoregulators. So the idea of suppressor/regulatory (Tsr) cells and of other suppressor cells (B cells etc.) was favored. Some suppressor cells work by cell-to-cell contact others secrete cytokines, (interleukin 10, FGF-beta) which does the job [23].

It is increasingly apparent that GC and KAT stimulate the growth of Tsr and of other suppressor cells. GC and KAT enhance the production of acute phase proteins and thus support the acute phase response (APR).

### Acute Illness

The first review of acute illness was published by Hans Selye. He proposed that "nocuous" stimuli (stressors) induce a stress response. Selye recognized that stressed animal exert a defence reaction, which he named the general adaptation syndrome [23]. Today the response to various noxious insults is called the Acute Phase Response (APR) [24,25].

Clinically APR is characterized by fever, loss of appetite, inactivity and sleepiness. Changes in sleep are hallmark of APR to infectious challenge. The regulation of these responses involves a cytokine cascade within the brain including IL-1 and TNF, and several other substances such as growth hormone releasing hormone, PRL. Nitric oxide (NO) and nuclear factor NF-kappa B. These substances also regulate normal sleep [26,27].

Endotoxin, infectious disease and various forms of injury elicit a systemic elevation of IL-1-beta, TNF-alpha and IL-6 which are secreted by cells of the innate immune system, primarily by monocyte-macrophages [28]. Colony stimulating factors (CSF) are cytokines originally stimulating the bone marrow [29]. The bone marrow is recognized today as a fundamental organ in natural immunity as it provides the leukocytes that fulfill this function.

The bone marrow is activated during APR which results in the generation of "leucocytosis" [30]. Recent studies indicate that Granulocyte-macrophage cytokines, (GM-CSF); macrophage cytokine, (M-CSF); and granulocyte cytokine (G-CSF); are involved in the

maintenance of host resistance to infectious disease [31,32] parasite infestation [33] and cancer [34,35].

GM-CSF has been proposed as a physiological regulator as it provided defence without much disturbance [36]. It stimulates adaptive immunity and immunological tolerance [37,38]. GM-CSF is used today for immunotherapy and for the production of recombinant vaccines [39,40].

In turn the cytokines stimulate the hypothalamus, the bone marrow, liver, and leukocytes directly or indirectly thus eliciting an APR [24,30,41]. Profound changes occur in serum hormone levels, the HPA axis is activated and there is also sympathetic outflow, which raises serum CAT levels. GC exerts a powerful suppressive effect on the adaptive immune system and also controls the level of inflammatory cytokines. However, the idea of having suppressor cells was much more compelling than was hormonal suppression of immunity. Suppressor/regulatory (T<sub>sr</sub>) cells and of other suppressor cells (B cell and so on) was confirmed. Some suppressor cells regulate by cell-to cell contact, others secrete cytokines, (interleukin 10, FGF-beta) which does the job [42].

Through the activation of the HPA axis and of the sympathetic nervous system, adaptive immune reactions are profoundly suppressed. Acute phase proteins are produced by the liver and natural antibody production is dramatically increased by a specific subset of B lymphocytes. Therefore the conversion of the immune system from the adaptive mode of reactivity to the amplification of natural immunity takes place [30,43-46].

PRL and GH stimulate the adaptive immune system and usually elevated within the first hour of endotoxin shock, which is followed by a decline and the level may become low normal to sub-normal in serious cases of endotoxin shock. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogens, androgens, progesterone, decline during infection and endotoxin shock, as a rule. Insulin, glucagon, alpha-melanocyte stimulating hormone, endorphin, leptin, corticotrophin releasing hormone (CRH) and arginine vasopressin are increase during endotoxemia [2,30,41]. It is clear that dynamic and diurnal changes of hormones should be taken into consideration when hormonal changes are considered in APR. Much remains to be done in this area.

A subset of marrow-derived macrophages in the brain, termed perivascular cells, synthesize prostaglandins after systemic cytokine or endotoxin challenges and play a critical role in the IL-1 induced HPA activation [47]. It has been also observed that peptidergic sensory nerves present in the vagus and elsewhere provide feedback signals to the brain about the sites of local inflammation [48].

## Acute-phase Proteins

Protein synthesis in the liver is altered in a major way during APR. The synthesis of acute phase proteins (APP) is dramatically enhanced, whereas some major normal proteins such as albumin and transferrin are significantly decreased. In patients with acute illness, C-reactive protein (CRP) and serum amyloid A (SAA) may increase over 1000-fold within 24-48 hrs. "fibrinogen-1" antitrypsin and certain complement and properdin components (e.g. factor B and C3) show a more moderate increase [41,49].

CRP binds to C-type pneumococcal cell walls in presence of Ca<sup>2+</sup>. It is present in multiple species of mammals, in fish and crab. CRP consists of five identical subunits which form a ring shaped molecule

named pentraxin, which also stands for a protein family [47]. CRP recognizes homotopes, which are frequently present on the surface of bacteria, fungi, parasites and in damaged cells and tissues. After combination with specific homotope, CRP activates complement with the classical pathway, which leads to enhanced chemotaxis, activation of phagocytosis by neutrophil leukocytes and macrophages. CRP stimulates the synthesis of IL-1, and TNF-alpha, and potentiates the cytotoxic activity of T-cells, NK cells and platelets. CRP localizes in sites of inflammation it binds to platelet derived growth factor (PAF) and blocks its activity. In the Clinics the presence of CRP in a patient means infectious, inflammatory disease [48,49]. Human CRP protects mice from otherwise lethal *Streptococcus pneumoniae* infection [50].

Lipopolysaccharide binding protein (LBP) shows 100 fold increase in the serum during APR. LBP can opsonize LPS binding particles. LPS activates complement by the alternative pathway. LBP-LPS binds complement and stimulate cytokines from monocyte-macrophages that bind CD 14 and toll-like receptor (TLR)-4. In humans high dose LBP suppressed the binding of both R-type and S-type LPS to CD14 and inhibited nuclear translocation of nFkappaB. LBP mediated the transfer of S-type LPS, to HDL.

Haptoglobin (HG) is an APP that binds hemoglobin, prevents iron loss and alleviates kidney damage. It is an antioxidant, anti-microbial and modulates the APR [51]. HG suppressed *in vitro* the production of TNF-alpha, IL-10, by LPS-stimulated monocytes. Did not inhibit IL-6, IL-8 and IL-1-receptor antagonist. HG knockout mice were sensitised to LPS [52].

The APP, alpha- (1)-acid glycoprotein and alpha(1)-antitrypsin exert anti-apoptotic anti-inflammatory effects and protect from ischemic kidney disease and from similar conditions [52].

Mannose-binding lectin (MBL) is an APP. It binds to sugar arrays present on many microorganisms. After binding MBL is activates the complement system via the serum protease, MASP-2. MBL mutations lead to frequent autoimmune disease such as systemic lupus erythematosus and rheumatoid arthritis [53]. GH regulates MBL levels [54].

Other APP-s proteinase inhibitors are alpha-2 macroglobulin, alpha-1 acid glycoprotein, antithrombin III, alpha-1 acute phase globulin, and alpha-1 proteinase inhibitor.

Kuppfer cells stimulate alpha-2 macroglobulin synthesis by hepatocytes in nitro in the presence of 10<sup>-9</sup> M Dexamethasone.

Fibrinogen is also an APP, important with blood coagulation and healing.

Alpha-macrotetoprotein (alpha-MFP) is a strong inhibitor of inflammatory mediators, such as histamine, bradykinin, serotonin, and prostaglandin E2. It also inhibits polymorphonuclear chemotaxis [40].

## Metabolic Effect of APR

Hyperglycemia, and lipolysis are characteristic of APR and catabolism prevails [55,56].

A clinical trial with GH on patients with acute illness did not reveal any advantage of GH. If anything significant, the mortality of treated patients was higher [57]. Apparently it is a mistake to use an anabolic hormone on a catabolic pathologic process. The disease may be aggravated.

Recently it was shown that GH treatment inhibited the production of APP in rats, and with burn injury of humans. This was also observed on human hepatocytes [58,59]. The above hypothesis is confirmed here to be true.

## The Regulation of APP

GC and KAT induce alpha-MFP, synergistically in normal rats [60]. GC stimulated hepatic APR by pro-inflammatory macrophage, migration inhibitory factor and secretion and the expression of cytokine, chemokine receptors [61]. Adrenaline induces a high level of IL-6, which may be inhibited by propranolol. When IL-6 is blocked the fast reacting APP, alpha-2 macroglobulin and cystein proteinase inhibitors are strongly depressed. Isoprenaline a beta-2 adrenergic receptor agonist also cause high levels of IL-6 [62].

IL-6 is a major inducer of APR. IFN-gamma, leukemia inhibitory factor, TGF beta, oncostatin M also induce APP from the liver. IL-6 activates the genes of APP through the DNA binding protein NF-IL-6. NF-IL-6 is a pleiotropic mediator serving many genes. The inducible genes are IL-6, IL-8 and several acute phase genes [63].

In humans IL-6 exerted a hyperglycemic effect, whereas IL-2 acted the opposite [64].

## Immunoconversion in APR

In APR the HPA axis and CAT are active. Glucocorticoids and CAT suppress the T-cell dependent adaptive immune system (ADIM). This suppression is further amplified by the suppression of hormones (PRL; GH; IGF-I), which support this system. APR induces apoptosis in the thymus with striking efficiency. The elevated levels of TNF-alpha, zinc deficiency, which develop during APR, also contribute to thymus involution and the suppression of ADIM [7,22].

## Healing

Febrile illness occurs on numerous occasions during a lifetime. Most of these diseases will heal and followed by recovery. We understand a lot about the pathological process, but know little about the healing process. Recent observations revealed that in chronic inflammation it is VP, and not CRH, is elevated. The implication is that VP coordinates recovery and also helps the healing process. VP is well suited for this action as it stimulates the HPA axis and also PRL, so that immune function may develop (immunostimulation) [7,65,66].

## Vasopressin and Stress

CRH and VP are released during stress by the elevated levels of epinephrine (EP) and norepinephrine. Seconds later the secretion of ACTH is induced, which elicits the secretion of GC by the adrenal cortex. CRH coordinates the endocrine, autonomic and behavioral and immune responses to stress and also acts as a neurotransmitter or neuromodulator in the amygdala, dorsal raphe nucleus, and hippocampus and locus coeruleus. VP, 5-hydroxytryptamine, CAT, substance P, vasoactive intestinal polypeptide, neuropeptide Y and cholecystokinin are produced in these loci. Cytokines, such as IL-1beta, TNF-alpha and IL-6, stimulate CRH and VP gene expression and are implicated in immune-neuroendocrine regulation. The expression profiles of CRH and VP genes are not uniform after stress exposure and the VP gene appears to be more sensitive to GC suppression [63,64].

Cytokine induced CRH and VP secretion is modulated by CAT, prostaglandins and NO [65].

Wistar and Lewis rats show differences in VP and CRH activity [66].

Elevated plasma VP levels were noted in patients with status asthmaticus during acute attack. The levels returned to normal with resolution of the acute phase [67]. MS patients were studied with normal controls. Patients with MS had higher cortisol levels but responded normally to ACTH stimulation with ovine CRH. The response to VP was blunted [68].

## Vasopressin in Chronic Inflammation

During chronic inflammation VP takes over as the regulator of the HPA axis [69]. Adjuvant arthritis in rats, EAE, eosinophilia-mialgia syndrome, systemic lupus erythematosus and leishmaniasis are such conditions. Only CRH can stimulate proopiomelanocortin (POMC), VP does not do this.

## VP and Cytokines

IL-1-beta, releases VP, this may be blocked by antibodies, atropine, or mecamylamine ACTH is also released [70].

IL-6 -induced ACTH was suppressed by both CRH and VP antisera [71].

TNF-alpha induced ACTH did not respond to anti-VP, but responded to anti-CRH antibodies [72].

IL-6 potentiated acetylcholine induced VP release [73].

Leukemia inhibitory factor administered centrally, significantly increased plasma VP, 5-60 min. after injection [74].

## Vasopressin in APR

VP attenuates the febrile response of rabbits to bacterial pyrogen [74]. Endotoxin may stimulate NO, which inhibits CRH, and generates carbon monoxide, which modulates the release of VP. These are potential counter regulatory controls of HPA activation [75].

LPS acts first within the median eminence where it stimulates peptidergic nerve terminals [76].

LPS potently stimulated CRH and VP secretion in pituitary blood of alert ewes. VP response was 10 times over CRH. Gonadotropin-releasing hormone and LH pulsation were suppressed and fever developed [77].

In Holstein steers LPS induced fever, increased plasma ACTH and cortisol. Pituitary VP receptor V3 mRNA was decreased at 2, 4 and 12 hrs following LPS injection, returned to normal by 24 hrs. Pituitary POMC-RNA did not respond [78].

## Regulation of Pituitary Hormones by VP

The ACTH response to exogenous application of VP was impaired in V1bR-/- mice, while CRH stimulated ACTH release. The increase of ACTH after forced swim stress was significantly suppressed in V1bR-/- mice [79].

In conscious male rats ICV infusion of histamine (HA) induced PRL secretion. This could be inhibited by antibodies and by VP

antagonist. This antagonist also inhibited the PRL response to restraint stress. An oxytocin (OT) antagonist had no effect [80].

VP antiserum suppressed the suckling induced rise in plasma prolactin [81]. Antisera to VP and vasoactive intestinal peptide completely abolished PRL release to suckling [82].

	Control	Sham	Sham+DP	Hypox	Hypox+DP	NIL	NIL+DP	NIL+TX
Adrenal weight		≠	↑↑↑	↓↓↓	↓	↑	↑↑	↑↑
Thymus weight		≠	≠	↓	↑Compared to Hypox	↓	≠	↓↓↓
Spleen weight		≠	↑↓	↓	↑Compared to Hypox	↑↓	≠ ↓	
Serum SRBC antibody		≠		↓↓		↓↓		
Serum SRBC C'Fixing antibody	↑↑	↑↑		↓↓		↓↓		
Serum IgG, IgM, anti-SRBC	↑↑	↑↑		↓		↓		
Arthus reaction (SRBC)	↑↑	↑↑		↓		↓		
Serum IgG, IgM; intestinal IgA, anti-	↑↑	↑↑		↓↓		↓		
Contact sensitivity to DNCB	↑↑	↑↑		↓		↓		
EAE: clinical score	↑↑	↑↑	↓	↑	↑↑↑	↓↓	↑↑	
EAE: plasma ACTH and corticosterone		↑	↑	↓↓↓↓	↓↓↓↓	≠		
Adenohypophyseal cell counts		≠				GH		TSH
						↓		↑↑↑
						LH		GH
						↓		↓↓↓↓
								PRL
								↓↓↓

aPlease see the text for a detailed explanation and for most abbreviations. Sham – sham –operated group of animals; Hypox – hypophysectomized animals; DP – desmopressin; NIL- neurointermediate pituitary lobectomy; SRBC – sheep red blood cells; C' – serum complement; Ig – immunoglobulin (G,M,A); DNCB – dinitrochlorobenzene; EAE- experimental autoimmune encephalitis; ACTH – adrenocorticotropin; GH – growth hormone; TSH – thyroid-stimulating hormone; LH- leutinizing hormone; PRL- prolactin; ↑ increase compared to intact control or sham operated control; ↓ decrease in relation to controls; ≠ no change with respect to the control; ↓↑ variable response. bGH, PRL, TSH and LH producing cell types were detected by immunocytochemistry.

**Table 1:** In long surviving rats (8 months), adrenal weight increased 30%, whereas thymus weight decreased 50% when compared to the intact control. Oral infection was used in the experiments with Salmonella typhimurium [7].

CRH or VP released ACTH and immunoreactive beta-endorphin response of HA and restraint stress. Pre-treatment with CRH antiserum abolished the ACTH response to 60%. Immunoneutralization by VP antiserum had half of the effect. CRH (100 pmol iv.) increased plasma ACTH and beta-endorphin. This effect was abolished by CRH antiserum, whereas VP antiserum abolished half of the effect. VP (2800 pmol iv.) stimulated ACTH and beta-END, in a dose dependent manner. CRH and VP antisera each prevented the VP-effect, whereas the beta-END response was 60% inhibited [83].

Endogenous VP and OT contribute to basal GH release, and play a significant stimulatory role in basal ACTH release [84].

The novel high-affinity nanopeptide, CRHR1antagonist, R121919, attenuates the stress induced release of corticosterone, PRL and OT. The decrease of testosterone after stress is abolished by R121919 [85].

In rats with paraventricular nucleus lesions LPS was able to activate the hypophysis-adrenal system in absence of hypophysis stimulating neuropeptides of paraventricular origin [86].

### Vasopressin and the Immune Response

Brattleboro diabetes insipidus (DI) rats derived from Long Evans rats (LE). DI rats lack VP, exhibit permanent decrease of blood lymphocytes, neutrophils are increased, macrophage activity is reduced, the thymus and spleen involuted early and antibody production was suppressed as well [87]. NK cell activity was higher

than LE rats. VP replacement normalized water intake in DI rats but this did not affect NK cell activity. DI rats exhibited lower plasma corticosterone, which was not affected by VP replacement [88].

In mice with the disruption of VP receptor (VPR1a) gene a shift was observed from IGM(high)/IGD(high) to the more mature IGM(low)/IGD(high) in B cell status. Splenic B cell proliferation was significantly greater with anti-IgM stimulation. IGG1 and IGG2b productions were enhanced in response to challenge with T-dependent antigen. T-cell differentiation and activation were normal in VPR (-/-) mice [89].

The VP-binding nonapeptide sequence is: Thr-Met-Lys-Val-Leu-Thr-Gly-Ser-Pro. VP and its 6 amino acid, N terminal cyclic ring, pressinoic acid (PA) are both capable of replacing the IL-2 requirement of IFN-gamma production in mouse splenic lymphocytes. The VP binding peptide specifically and reversibly blocked VP help in IFN-gamma production but failed to block the helper signal of PA. Thus the intact VP molecule and not just the N-terminal cyclic ring are important for interaction with the binding peptide [90,91].

VP enhanced the mixed lymphocyte reaction. Enhanced proliferation, which appeared to be specific for the arginine residues, is at position 8 of VP [92].

VR1 receptor antagonist induced a complex intracellular Ca<sup>2+</sup> signaling cascade event in cortical astrocytes. It dramatically reduced the mRNA response to five cytokines including IL-1-beta and TNF-alpha [93].

### Our Observations

Membrane VP receptors are present in several immune cell type [89,94,95]. We investigated the effect of neurointermediate pituitary lobectomy (NIL) on the immune function of rats. NIL rats have low plasma level of VP and OT [96].

Parameter	CRH	VP
Pituitary adrenal axis	↑↑↑	↑↑
POMC	↑↑↑	0
Prolactin	↓↓	↑↑
Cytokines	IL-1,6 TNF-α	IL-1,2,6 LIF
Adaptive Im.	↓↓↓	↑↑↑
Autoimmunity	↓↓↓	↑permissive
Chronic inflam.	↓↓↓	↑↑
Nat. Imm., APR	↑↑↑	↑↑↑
LPS response	↑↑↑	↑↑↑

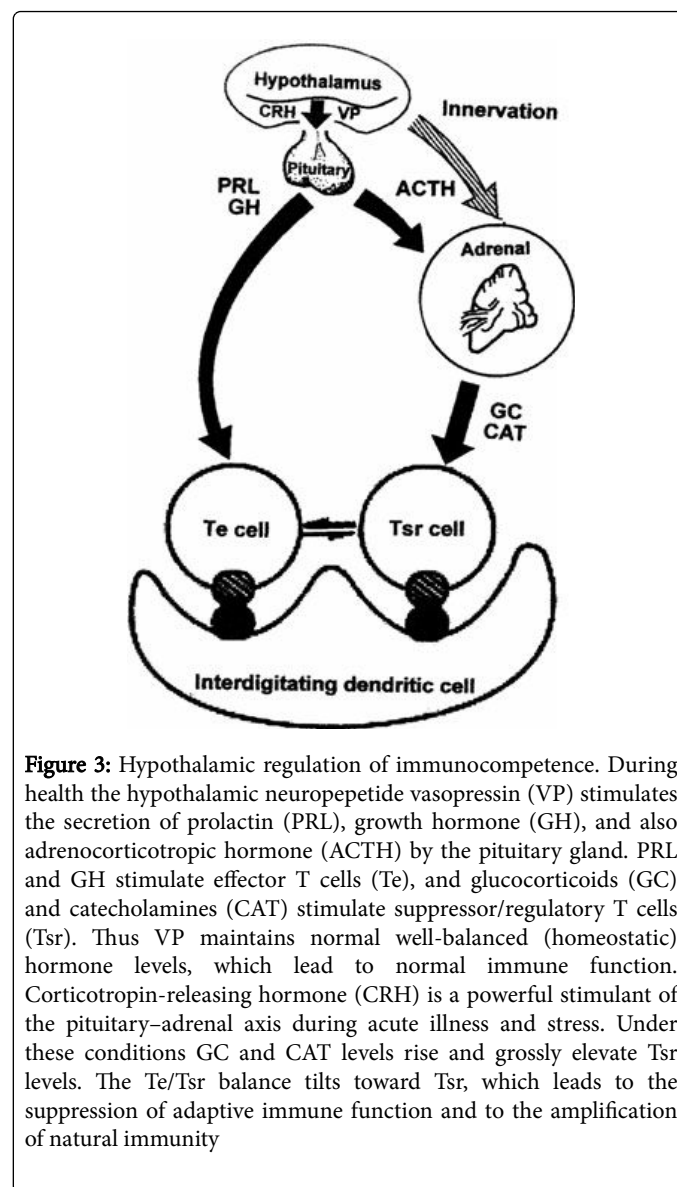
CRH: Corticotrophin Releasing Hormone; VP: Vasopressin; POMC: Proopiomelanocortin; IL: Interleukin; TNF: Tumor Necrosis Factor; LIF: Leukemia Inhibitory Factor; APR: Acute Phase Response; LPS: lipopolysaccharides.

**Table 2:** Hypothalamic Immunoregulation.

The adrenal glands are enlarged in some experiments but not in others [97,98]. If thyroidectomy was also done in NIL animals, the adrenal glands are enlarged in NIL rats the increase of adrenal size and decrease in thymus and spleen weights was observed. NIL inhibited Immune function including IgG and IgM responses too sheep red

blood cells [99]. Plasma IgG and IgM and intestinal secretion of IgA antibodies to Salmonella tyhimurium were inhibited [100]. Delayed type hypersensitivity to dinitrochlorobenzene (DNCB) and the Arthus reaction could not be induced in NIL rats. The incidence and severity of EAE [17] was reduced. And there was failure to develop adjuvant arthritis [101].

Using EAE in NIL animals we studied desmopressin (DP), a synthetic analog of VP. Immune-inflammatory responses and HPA axis were studied. DP antagonized the NIL effect. It restored EAE reactivity in NIL animals which was accompanied with high ACTH and Cortisol levels (Tables 1 and 2 and Figure 3).



**Figure 3:** Hypothalamic regulation of immunocompetence. During health the hypothalamic neuropeptide vasopressin (VP) stimulates the secretion of prolactin (PRL), growth hormone (GH), and also adrenocorticotrophic hormone (ACTH) by the pituitary gland. PRL and GH stimulate effector T cells (Te), and glucocorticoids (GC) and catecholamines (CAT) stimulate suppressor/regulatory T cells (Tsr). Thus VP maintains normal well-balanced (homeostatic) hormone levels, which lead to normal immune function. Corticotrophin-releasing hormone (CRH) is a powerful stimulant of the pituitary-adrenal axis during acute illness and stress. Under these conditions GC and CAT levels rise and grossly elevate Tsr levels. The Te/Tsr balance tilts toward Tsr, which leads to the suppression of adaptive immune function and to the amplification of natural immunity

### Conclusions

This overview indicates that VP is a major immunoregulator, more versatile than CRH. CRH is specific for APR and regulates proopiomelanocortin. VP supports the APR but its major role is to take care of healing and also regulates immune function during healthy life. VP is the number-1 hypothalamic hormone we need every day of our

life. These observations promise a better understanding of illness and recovery to significantly aid patient management.

More studies are needed for better understanding of this subject.

## Acknowledgements

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This paper is a shortened version of paper no 101. Because the original work is a highly concentrated text, it was not possible to reword definitions and such portions of the text that are irreplaceable. So here we would like to give credit to the original paper. I am satisfied that this story will be presented for the second time.

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