Sem IV (PG)

Paper ZOO-402

Group B : Neuro-Immuno Endocrinology

Prepared by Anindita Das

Neuro-immuno endocrine pathways (3)

Interaction between the neuroendocrine and immune systems

THE CELLS OF THE IMMUNE SYSTEM:

- MONOCYTES AND MACROPHAGES

Monocytes develop from precursor cells in the bone marrow and travel through the bloodstream to various tissues where they mature into macrophages. Macrophages phagocytose and break down foreign antigens and present epitopes of these antigens to T cells. Macrophages also synthesize and release the cytokine, IL-1.

- T LYMPHOCYTES (T CELLS)

The precursor cells for the T lymphocytes are produced in the bone marrow and migrate to the thymus gland through the circulatory system. In the thymus gland, the T cell precursors differentiate to form Th cells, Tc cells and Ts cells. Tc cells destroy body cells that have been infected by viruses, tumor cells, and foreign cells. Th cells release cytokines which stimulate the immune functions of other lymphocytes. Ts cells are able to suppress immune responses by inhibiting the actions of Th and Tc cells. After the T cells mature in the thymus gland, they are stored in the secondary lymph organs, e.g. the spleen, lymph nodes and Peyer's patches before being released to circulate through the body.

- B LYMPHOCYTES (B CELLS)

As with T cells, the precursors of the B lymphocytes are produced in the bone marrow. In mammals, the B cells mature in the bone marrow and then migrate

to the secondary lymph organs, where they are stored and released into the circulation. In birds, B cells mature in the bursa of Fabricius before being stored in the secondary lymph organs. The committed B cells are antigen specific and produce antigen-specific antibodies which bind to the antigens and inactivate them. With antibody-producing B cells, they also produce 'memory' B cells.

- NATURAL KILLER (NK) CELLS

NK cells are large lymphocytes which develop in the bone marrow. They are stored in the secondary lymph organs, from which they are released to circulate in the bloodstream. NK cells are able to spontaneously kill virus-infected cells and tumor cells. NK cells also release interferon γ (IFN γ).

- GRANULOCYTES

Granulocytes are mature granular leukocytes (WBCs). There are three types of granulocyte: neutrophils, eosinophils and basophils. Neutrophils destroy dead cells, bacteria and other foreign cells by phagocytosis. Eosinophils destroy parasites and modulate inflammatory responses in damaged tissues. Basophils destroy parasites by phagocytosis and are involved in immediate hypersensitivity (i.e. allergic) reactions through their secretion of histamine.

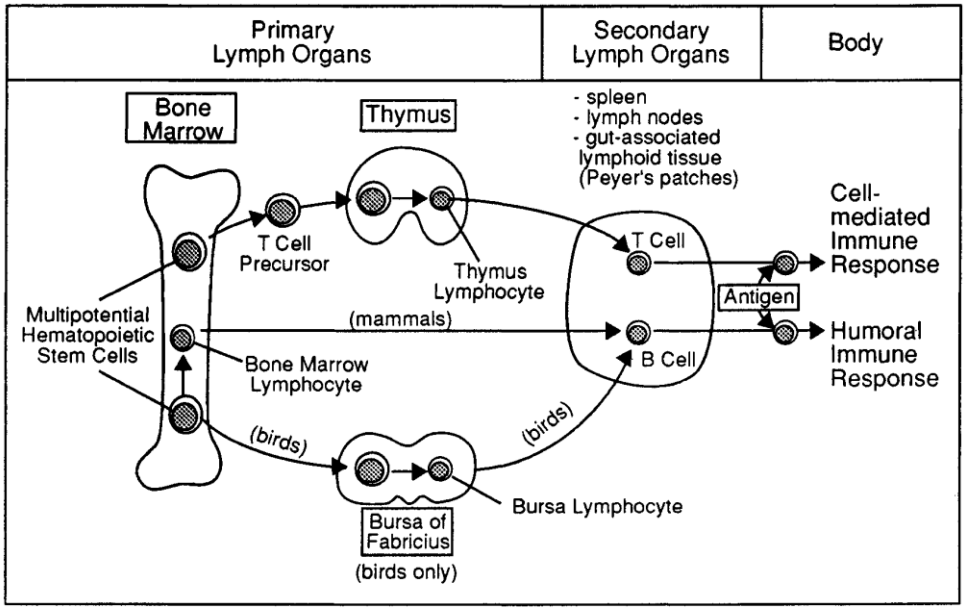

Fig 14: The development of T and B cells. Multipotential HSCs in the bone marrow produce the precursors of both T and B lymphocytes. In both mammals and birds, the precursors of the T lymphocytes migrate from the bone marrow through the bloodstream to the thymus gland, where they differentiate into thymus lymphocytes. When the thymus lymphocytes mature, they migrate to secondary lymph organs to become thymus-derived lymphocytes (T cells) which regulate immune responses. In mammals, the precursor cells destined to become B cells differentiate into lymphocytes in the hematopoietic tissue of the bone marrow and then migrate to secondary lymph organs to become B cells, which produce antibodies for the humoral immune responses. In birds, B cell precursors migrate to the bursa of Fabricius, where they differentiate into bursa lymphocytes. Many of these lymphocytes die, but others migrate to secondary lymph organs to become bursa-derived lymphocytes (B cells).

THE THYMUS GLAND AND ITS HORMONES

The thymus is a two-lobed gland which is located in the chest, above the heart. It has two regions: one in which the T lymphocytes mature, and one containing epithelial cells, which secrete the thymic hormones. The thymus gland produces at least ten peptide hormones, which are collectively referred to as the thymic hormones. These include **thymosin a, thymosin b, thymosin fraction 5, thymopoietin, thymic humoral factor and serum thymic factor**.

The thymus has been called 'the master gland of the immune system' because its hormones are essential for both cell-mediated and humoral immunity. The thymic hormones facilitate the production of T cell precursors in the bone marrow, regulate the differentiation into Th, Tc and Ts cells in the thymus gland and activate mature T cells in the spleen and lymph nodes (Figure 15). Thymic hormones also mobilize NK cells and stimulate the release of cytokines from macrophages and Th cells. The activity of the thymus gland is mediated by autonomic nerve pathways as well as pituitary, adrenal, thyroid and gonadal hormones. The thymus gland is particularly sensitive to adrenal and gonadal steroids. In turn, the thymic hormones act on both neural and endocrine cells. The thymus gland is essential for the maturation and differentiation of T cells and the development of cell-mediated immune responses in newborn animals. In most mammals, the absolute size of the thymus gland increases until puberty, after which it begins to decline in both size and function. As the size of the thymus gland declines, the level of thymic hormones in the blood and the ability to exhibit thymus-dependent (T cell) immunity. As a result, there is an increase in diseases associated with failure of the cell-mediated immune system (e.g. cancer and infectious diseases) as aging occurs.

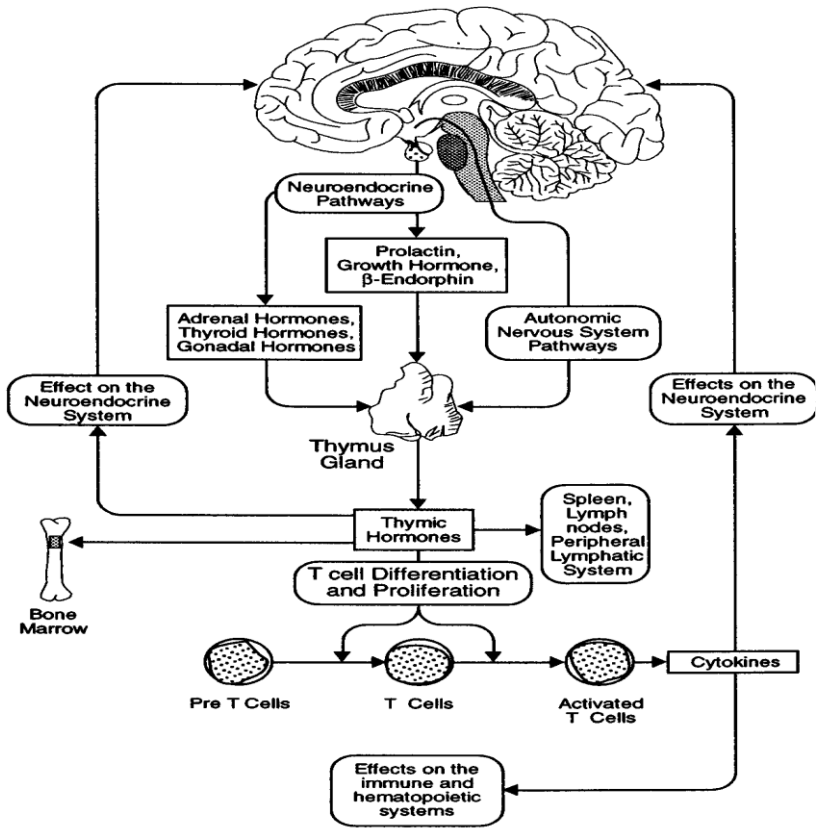

Fig 15: The interactions between the thymus gland and the neuroendocrine system. Thymus gland development and thymic hormone release is regulated by hormones from the pituitary, adrenal gland and gonads, and by the autonomic nervous system. The thymic hormones regulate T cell precursor development in the bone marrow, the differentiation and proliferation of T cells in the thymus gland and the maturation of the T cells in the secondary lymph organs. Both the thymic hormones and the cytokines released from activated T cells have effects on the brain and neuroendocrine system as well as on the immune and hematopoietic systems.

CYTOKINES: THE MESSENGERS OF THE IMMUNE SYSTEM

Cytokines are protein messengers which are produced and released by macrophages, T cells, B cells, and other cells of the immune system when these cells are activated by antigen presenting cells, neural stimulation or hormones. Cytokines communicate between the cells of the immune system and are essential for the activation of immune responses and the development of blood cells (haematopoiesis). Cytokines may be considered as hormones, since they are produced in one cell and may travel through the blood to act at distant cells. Cytokines also have paracrine and autocrine actions. When first discovered, cytokines were named according to their function (e.g. T cell growth factor) and classified as lymphokines or monokines. However, it soon became clear that each cytokine had a number of different functions and that two or more cytokines often served the same function. To reduce the confusion, individual cytokines were named interleukins, based on their ability to communicate between leukocytes. As the structure and function of individual cytokines was identified, they were reclassified as shown in Table 1. Each cytokine has its own specific receptors on the surface of its target cells and the synthesis of these receptors is usually activated at the same time as the synthesis of the cytokines. Like the receptors for the peptide hormones, cytokine receptors are coupled to G-proteins and activate second messenger systems within the target cell. These second messengers include cAMP, Ca^{2+} and the other second messengers. After the cytokine binds to its receptor, the entire complex is taken into the cell (internalization) and degraded by lysosomes, thus deactivating both the cytokine and its receptor. When the stimulus for cytokine synthesis is removed, downregulation of receptors also occurs. Furthermore, one cytokine may stimulate the synthesis and release of a second cytokine, whose biological effects may be ascribed to the first cytokine! Since each cytokine may have several functions, and each bioassay usually detects only one of these, it is difficult to characterize all of the different functions of each cytokine.

Table 1: Examples of some cytokines, their source and functions:

Cytokine	Cellular source	Function
Interferon γ (IFNγ)	Activated T cells	Activates macrophages Stimulates B cell proliferation and differentiation Stimulates IL-2 synthesis
Interleukin 1 (IL-1α and β) (Lymphocyte activating factor)	Macrophages, T cells, B cells, NK cells, fibroblasts, etc.	Enhances T and B cell activation Promotes proliferation of T and B cells Stimulates prostaglandin synthesis Causes inflammation and fever Stimulates synthesis of IFNγ, IL-2, IL-3 and IL-4
Interleukin 2 (IL-2) (T cell growth factor)	Activated T cells	Stimulates T cell growth Activates cytotoxic T cells Stimulates B cell growth and proliferation Stimulates growth of NK cells
Interleukin 3 (IL-3) (hematopoietic cell growth factor)	Macrophages, activated T cells	Stimulates growth and differentiation of cells produced by the hematopoietic stem cells
Interleukin 4 (IL-4) (B cell stimulation factor 1)	Macrophages, activated T cells	Promotes T cell growth Stimulates B cell proliferation and differentiation Activates macrophages
Interleukin 5 (IL-5) (B cell growth factor 2)	Activated T cells	Promotes B cell proliferation Stimulates antibody production
Interleukin 6 (IL-6) (B cell stimulation factor 2)	Monocytes, activated T and B cells, fibroblasts	Promotes B cell proliferation and differentiation Activates T cells Induces fever and inflammation
Tumor necrosis factor (TNF)	Macrophages, T cells, B cells	Destruction of tumor cells Mediates endotoxic shock reaction Inhibits feeding Causes cachexia (wasting)
Lymphotoxin (LT) (tumor necrosis factor β)	Activated T cells	Destruction of tumor cells
Colony stimulating factors (CSFs)	Fibroblasts, monocytes	Stimulate growth and differentiation of hematopoietic stem cells in bone marrow

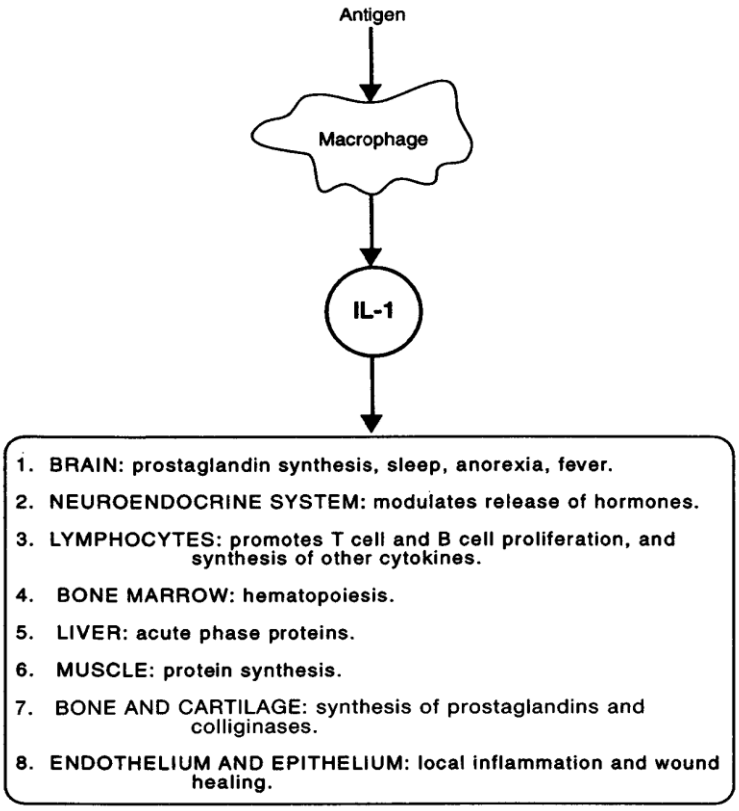

Fig 16: Some of the actions of interleukin 1 (IL-1). As well as its actions on the lymphocytes and bone marrow, IL-1 has receptors in the brain, liver, muscle, skin and bone and has a number of actions on these non-immune cells.

Example of one cytokine is shown.

EFFECTS OF CYTOKINES AND OTHER IMMUNOMODULATORS ON THE BRAIN AND NEUROENDOCRINE SYSTEM

As shown in Figure 17, the cells of the immune system can communicate with the brain and neuroendocrine system through the production of cytokines and through the synthesis and release of peptide hormones. Although Hall et al. (1985) suggested that the messengers of the immune system, including the cytokines, peptide hormones and thymic hormones, be termed 'immunotransmitters', it is more appropriate to call them 'immunomodulators' (Plata-Salaman, 1989) or 'immunoregulators' (Plata-Salaman, 1991) because they have modulator rather than transmitter actions on the brain and endocrine system.

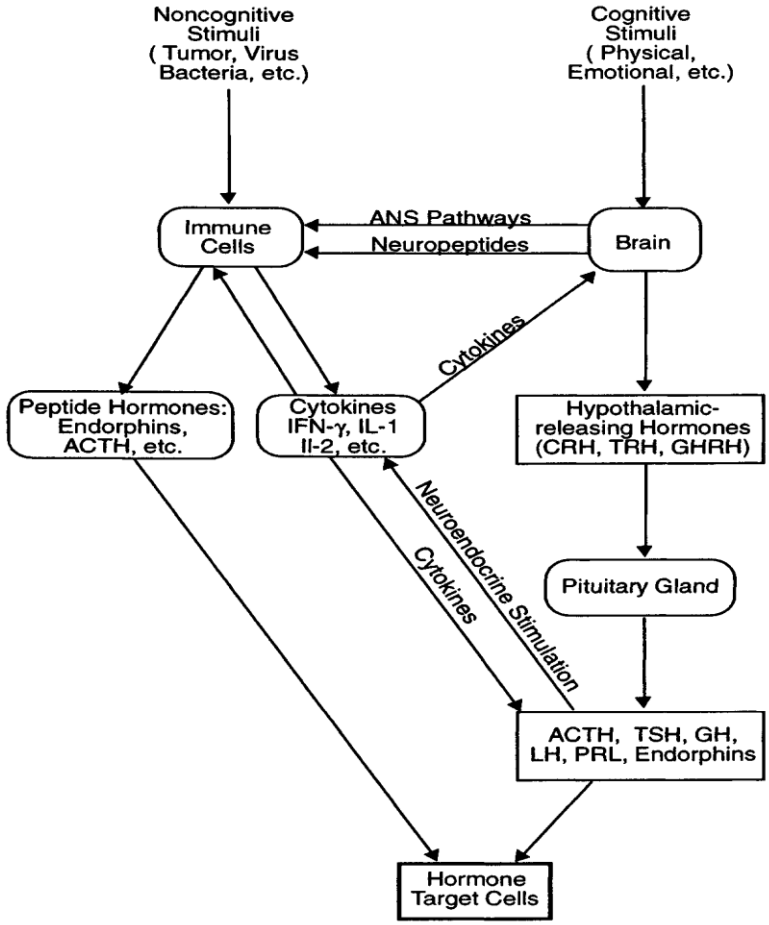

Fig 17: Inter-communication among the neural, endocrine and immune systems. The immune system is sensitive to non-cognitive stimuli, such as bacteria and viruses, which are not perceived by the central nervous system. Upon activation, cells of the immune system secrete cytokines and peptide hormones. The cytokines action on the brain and neuroendocrine system as well as on other immune cells. The peptide hormones released from the immune cells may stimulate immune cells or endocrine cells. Perception of cognitive stimuli by the brain can result in stimulation of the cells of the immune system by the peripheral nerves of the autonomic nervous system, the release of neuropeptides, or through the activation of the neuroendocrine system. In this way, the brain can indirectly perceive the presence of bacteria and viruses. One of the functions of the immune system, in fact, may be to make the brain aware of these stimuli through the release of cytokines.

- *LOCALIZATION OF CYTOKINES AND THEIR RECEPTORS IN THE BRAIN*

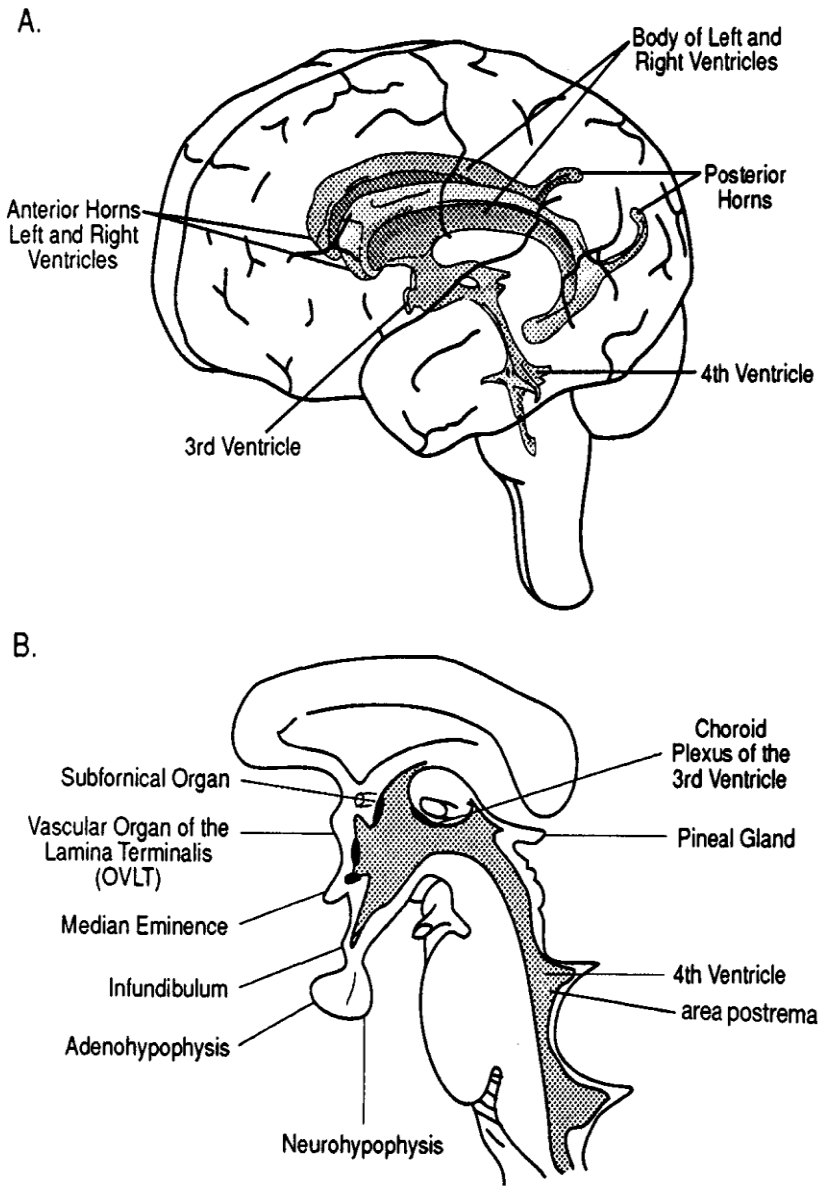

Fig 18: The ventricles and the circumventricular organs of the human brain. (A) The locations in the brain of the main body and the anterior and posterior horns of the right and left ventricles are shown, as well as the positions of the third and fourth ventricles. (B) The circumventricular organs of the third ventricle. The capillaries of the choroid plexus are fenestrated and most cerebral spinal fluid is produced in this organ. The pineal gland, subfornical organ, vascular organ of the lamina terminalis (OVLT), median eminence and neurohypophysis also contain fenestrated capillaries which allow free communication between the blood and the extracellular fluid of the brain.

Table 2: Distribution of some cytokines, their receptors and second messenger systems they act through:

Cytokines	**Distribution in brain**	**Receptors in brain**	**Second messenger systems**
IL - 1	Infundibulum, median eminence, periventricular nucleus and other nuclei	Olfactory bulbs, dentate gyrus, hippocampus, hypothalamus and choroid plexus	Inositol phospholipid, PK - C
IL - 2	VMN (Ventromedial Nucleus), PVN (Paraventricular Nucleus)	hippocampus, striatum, and frontal cortex	-
IL - 3	Near the circumventricular organs	olfactory bulbs, hippocampus and cortex	Tyr kinase, PK - C
IL - 6	Throughout the hypothalamus	-	Cyclic AMP (cAMP)

- *EFFECTS OF 'IMMUNOMODULATORS' ON THE NEUROENDOCRINE SYSTEM*

  Cytokines modulate the firing rate of neurons, thus altering the release of neurotransmitters and regulating the ANS, the neuroendocrine system, and the cognitive and behavioural functions of the brain. Cytokines modulate the neuroendocrine functions of the hypothalamus as well as acting on the pituitary, thyroid, pancreas, adrenal glands and gonads to modulate hormone release.

Table 3: Effects of cytokines and thymic hormones on the release of pituitary hormones

	Pituitary hormones						
Cytokine	GH	PRL	ACTH	TSH	LH	FSH	β-END
Interferon γ	–	0↑	↑	↓	–	–	–
IL-1	↑↓0?	↑↓0?	↑	↑↓?	↑↓?	0	↑
IL-2	–	–	↑	–	–	–	↑
IL-6	↑	↑	↑	↑	↑	–	↑
TNF	↑↓0?	↑	↑	↓	–	–	↑
Thymic hormones	↑0?	↑0?	↑	0	↑	0	↑

↑ = stimulates release; ↓= inhibits release; 0 = no effect; ? = conflicting results; -=not tested or unknown, END –endorphin.

- *THE PRODUCTION OF PEPTIDE HORMONES BY CELLS OF THE IMMUNE SYSTEM*

  As shown in Table 4, many cells of the immune system are able to synthesize and release peptide hormones which are identical with those produced in the hypothalamus and pituitary gland. For example, the thymus gland produces oxytocin and vasopressin, while leukocytes and mast cells produce somatostatin and vasoactive intestinal peptide (VIP). T cells can synthesize endogenous opioids, TSH and human chorionic gonadotropin, while lymphocytes produce GH and prolactin, as well as ACTH and β-endorphin. Both leukocytes and spleen cells produce LH, and other peptides. The peptide hormones are released from the cells of the immune system in response to stimulation from both antigens and hypothalamic hormones. For example, viral infections stimulate ACTH and β-endorphin release from lymphocytes, macrophages, and spleen cells. Lymphocytes, monocytes and macrophages all have CRH receptors and produce ACTH and β-endorphin in response to CRH release from the hypothalamus. The synthesis of these hormones by cells of the immune

system is inhibited by glucocorticoids, indicating that hormone release from immune cells is regulated by negative feedback as it is in pituitary corticotroph cells. Thus, the 'stress-induced' release of ACTH and β-endorphin can be stimulated from the pituitary gland by cognitive stimuli and from the cells of the immune system by noncognitive stimuli (see Figure 17).

Table 4: Hormones synthesized and released from cells of the immune system

Cells	Hormones released
Thymus	Oxytocin, vasopressin
T cells	Enkephalins, TSH, hCG
Lymphocytes	CRH, ACTH, β-endorphin, GH, prolactin
Monocytes	ACTH, β-endorphin, substance P, somatostatin
Macrophages	ACTH, β-endorphin
Leukocytes	VIP, somatostatin, LH, FSH
Spleen cells	ACTH, LH