Sem IV (PG)

Paper ZOO-402

Group B : Neuro-Immuno Endocrinology

Prepared by Anindita Das

Neuro-immuno endocrine pathways (4)

NEURAL AND ENDOCRINE REGULATION OF THE IMMUNE SYSTEM

As outlined in Figure 17, the neural and endocrine systems can modulate the immune system in three different ways: (1) through the autonomic nervous system (ANS) pathways; (2) through the release of hypothalamic and pituitary hormones; and (3) through the release of neuropeptides.

(1) AUTONOMIC NERVOUS SYSTEM INFLUENCES ON THE IMMUNE SYSTEM:

The autonomic nervous system innervates all of the tissues of the immune system shown in Figure 14: the bone marrow, the thymus gland, spleen and lymph nodes. Both the sympathetic (adrenergic) and the parasympathetic (cholinergic) branches of the ANS innervate immune tissues.

- **Adrenergic stimulation**

In the bone marrow, catecholamines facilitate the production of multipotential stem cells, the precursors of both T cells and B cells. T cells, B cells and macrophages have β-adrenergic receptors. Adrenergic stimulation promotes the differentiation and maturation of T cells, the growth of Tc cells and the production of antibodies by B cells. Adrenergic stimulation also regulate the release of the thymic hormones, which stimulate the developing T lymphocytes by paracrine action. This suggests that the thymus gland acts as a neuroendocrine transducer, responding to neural stimulation from the adrenergic nerves of the sympathetic nervous system (SNS) by releasing thymic hormones.

Along with the catecholamines, the sympathetic branch of the SNS coreleases a number of neuropeptides, including VIP, CCK, neuropeptide Y, somatostatin, and others. These neuropeptides also regulate the action of the immune system.

- **Cholinergic stimulation**

Cholinergic stimulation of the immune system is less pronounced than adrenergic stimulation, but cholinergic receptors have been found in the epithelial cells of the thymus and in the bone marrow. Only the sympathetic branch of the ANS innervated the thymus gland. T lymphocytes have cholinergic as well as adrenergic receptors. The most common effect of acetylcholine in the immune system is the activation of T cell proliferation, but acetylcholine may also accelerate the synthesis of antibodies by B cells. Table 5 provides an overview of the effects of the autonomic nervous system and the neuroendocrine system on the immune system.

(2) EFFECTS OF HYPOTHALAMIC AND PITUITARY HORMONES ON THE IMMUNE SYSTEM

All of the hypothalamic and pituitary hormones modulate the immune system, as have the hormones of the adrenal cortex, thyroid gland and the gonads. Cells of the immune system have receptors for more than 20 hormones and neuropeptides.

- **Neurohypophyseal hormones:**

Both oxytocin and vasopressin act on the thymus gland where they modulate the synthesis and secretion of thymic hormones and may thus function as T cell growth factors. Since oxytocin and vasopressin are both synthesized in the thymus, they act in a paracrine manner in this gland. Oxytocin and vasopressin may also stimulate the release of interferon γ from Tc cells and act to regulate hormone production by the cells of the immune system.

- **GH and prolactin:**

GH and prolactin have wide-ranging effects on the immune system. GH stimulates the growth of the thymus gland and the proliferation and differentiation of T cells and modulates the actions of macrophages, B cells, and NK cells. Prolactin enhances the responsiveness of the immune system by stimulating cytokine release from Th cells. Prolactin and GH are also able to restore thymic function and T cell activity in aged mammals.

- **The hypothalamic-pituitary-thyroid system:**

TRH and TSH enhance the activity of the immune system by stimulating spleen cells and T cells. TSH increases antibody production and may do this by

stimulating cytokine release from T cells. Thyroid hormones (T3 and T4) also stimulate the release of thymic hormones and the maturation of T lymphocytes.

- **The hypothalamic-pituitary-gonadal system:**

The hormones of the hypothalamic-pituitary-gonadal system modulate the immune system in a number of ways. The cells of the immune system have receptors for the gonadal steroids and the immune response is altered during pregnancy. Because steroid hormone levels rise at puberty, the sex differences in immune responsiveness may be more obvious after puberty.

There are sex differences in the structure of bone marrow, the level of antibodies in the circulation, and in susceptibility to autoimmune diseases, infectious diseases and cancer. Female spleen cells produce more IL-2 (T cell growth factor) than male spleen cells and T cells from females are more responsive to IL-2 than those from males. Females have higher serum antibody levels than males and develop stronger and longer lasting immune responses to antigens. Women are more prone to autoimmune diseases such as rheumatoid arthritis, in which 70% of the patients are female, and systemic lupus erythematosus (an autoimmune disease, which resembles rheumatoid arthritis and can affect many different organs and tissues), in which 90% of the patients are female.

In general, the gonadal steroids inhibit cell mediated immunity. Like the corticosteroids, androgens and estrogens suppress thymus activity. High levels of estrogens also suppress T cell and NKcell activity. The sex hormones may inhibit cell-mediated immunity by inhibiting the release of thymic hormones, thus inhibiting T cell development. On the other hand, ovarian steroids, particularly estrogen, facilitate humoral immunity. Estrogens stimulate the production of antibodies. Estrogens also enhance phagocytosis by macrophages.

In human females, the activity of the immune system changes over the menstrual cycle. The levels of lymphocytes and WBCs in the circulation are negatively correlated with estrogen levels, while the levels of monocytes and granulocytes are positively correlated with progesterone levels. Finally, estrogens appear to activate autoimmune diseases while androgens may inhibit the development of autoimmune diseases.

During pregnancy, the increased levels of gonadal steroids (as well as pituitary and placental gonadotropic hormones) suppress cell-mediated immune responses, thus help to prevent the rejection of the fetus (which is 'foreign

tissue'). HCG, for example, is able to inhibit Tc cell and NK cell activity and increase the activity of Ts cells, either by direct immunosuppressive action on these cells or by stimulating progesterone secretion. The size of the thymus gland and the number of T cells are both reduced during pregnancy. If this depression of cell-mediated immunity does not occur during pregnancy, the fetus may be aborted.

- **The hypothalamic-pituitary-adrenal system:**

All three hormones of the hypothalamic-pituitary-adrenal system (CRH, ACTH, and the glucocorticoids) modulate immune system activity. CRH stimulates the production of IL-1 by monocytes, increases the proliferation of T cells, stimulates the release of IL-2, and promotes the upregulation of IL-2 receptors on helper T cells. ACTH inhibits the production of IFNγ by T cells and inhibits the production of IFNγ receptors on macrophages, thus blocking IFNγ activation of macrophages. ACTH also promotes B cell proliferation, but inhibits antibody production.

Glucocorticoids have wide-ranging effects on the immune system. In general, the glucocorticoids inhibit immune system function, but they also have some stimulatory effects. Corticosteriods inhibit the ability of macrophages to phagocytose foreign tissue and inhibit the release of cytokines from macrophages. Corticosteriods also suppress cellular immunity by inhibiting thymus gland development, inhibiting the release of thymic hormones, and inhibiting the development and differentiation of T cells in the thymus gland. Glucocorticoids inhibit the release of IL-1 from macrophages, inhibit the release of IFNγ and IL-2 (T cell growth factor) from T cells, and inhibit the release of colony stimulating factors, thus inhibiting the development of monocyte (pre-macrophage) colonies in bone marrow. By inhibiting IL-2 release, glucocorticoids inhibit the development of cytotoxic T cells, but once these cells mature, they are resistant to the inhibitory effects of corticosteroids. Corticosteroids also inhibit the activity of NK cells.

Many of the effects of corticosteroids on the immune system are biphasic. For example, there is an initial inhibition of macrophage and T cell development when corticosteroids are released following a stressor stimulus, but the prolonged release of corticosteroids may stimulate the immune response. These biphasic responses to corticosteroids may also depend on the level of corticosteroids in the blood.

- **Corticosteroids as negative feedback signals for the immune system:**

Since cells of the immune system produce cytokines (such as IL-1) and ACTH, both of which stimulate corticosteroid release, and since corticosteroids inhibit the activity of the immune system, it has been hypothesized that the immunosuppressive action of corticosteroids acts to provide negative feedback in the immune system, the immunosuppressive action of corticosteroid negative feedback may prevent the development of autoimmune diseases such as rheumatoid arthritis, in which the immune system attacks and destroys self-cells as well as foreign cells.

(3) EFFECTS OF NEUROPEPTIDES ON THE IMMUNE SYSTEM

As well as the hypothalamic and pituitary hormones, a number of neuropeptides modulate the activity of the immune system and the release of cytokines (Table 5). These include substance P, somatostatin, the endogenous opioid peptides, vasoactive intestinal peptide (VIP) and nerve growth factor (NGF). These neuropeptides may be secreted from neurosecretory cells in the brain or co-released with neurotransmitters from neurons in the brain and peripheral nerves of the autonomic nervous system (ANS). The thymus gland has receptors for β-endorphin, the enkephalins and substance P and T lymphocytes have receptors for somatostatin, VIP and substance P.

β-endorphin and the enkephalins modulate the synthesis of IFNγ, enhance NK cell activity, promote B cell proliferation and stimulate the production of thymic hormones. β-Endorphin enhances antibody production by B cells, while the enkephalins suppress antibody production.

Substance P promotes phagocytosis by macrophages, stimulates T cell proliferation and stimulates antibody production by B cells. Somatostatin, on the other hand, inhibits T lymphocyte proliferation, inhibits colony stimulation in bone marrow, and inhibits antibody production by B cells. VIP inhibits T cell proliferation and the production of IL-2, inhibits NK cell activity and has a number of other regulatory effects on the immune system. Nerve growth factor (NGF) is released by the adrenergic neurons of the SNS which innervate the bone marrow, thymus gland, spleen and lymph nodes, and can influence the development of lymphocytes in these organs. NGF stimulates the proliferation and differentiation of lymphocytes and stimulates the release of IL-2 from T cells.

Table 5: Summary of neural and hormonal effects on the immune system

Neuroendocrine stimulus	Effects on immune system
Autonomic nervous system activity	
Adrenergic stimulation	Inhibits macrophage activity Stimulates multipotential stem cell development Stimulates T cell proliferation Stimulates antibody production from B cells
Cholinergic stimulation	Stimulates multipotential stem cell development Enhances T cell proliferation Stimulates antibody production from B cells
Hypothalamic–pituitary (H-P) hormones	
Oxytocin and vasopressin	Enhance T cell growth
GH and PRL	Enhance T cell proliferation and differentiation
H-P-thyroid system (TRH and TSH)	Stimulate T cell maturation Stimulate antibody production from B cells
H-P-gonadal system	
Estrogen	Stimulates macrophage activity Suppresses T cell proliferation Stimulates antibody production from B cells
Testosterone	Inhibits T cell proliferation Inhibits antibody production from B cells
Progesterone	Inhibits development of multipotential stem cells Inhibits macrophage activity Inhibits T cell proliferation Inhibits antibody production from B cells
HCG	Inhibits cytotoxic T cell activity Stimulates suppressor T cell activity Inhibits natural killer cells
H-P-adrenal system	
ACTH	Inhibits macrophage activity Inhibits T cell proliferation Stimulates B cell growth, but inhibits antibody production
Glucocorticoids	Inhibit multipotential stem cell colony formation Inhibit phagocytosis by macrophages Inhibit T cell proliferation and cytotoxic T cell activity Inhibit antibody production from B cells Inhibit natural killer cell activity
Neuropeptides	
Substance P	Stimulates phagocytosis by macrophages Stimulates T cell proliferation Stimulates antibody production from B cells
Somatostatin	Inhibits multipotential stem cell colony formation Inhibits T cell proliferation Inhibits antibody production from B cells
Endogenous opioid peptides (β-endorphin, enkephalins)	Inhibit phagocytosis by macrophages. Stimulate T cell proliferation and cytotoxic T cell activity Stimulate (β-endorphin) or inhibit (enkephalins) antibody production from B cells (depending on the state of the cell) Stimulate natural killer cell activity
VIP	Inhibits phagocytosis by macrophages Inhibits T cell proliferation Inhibits antibody production from B cells Inhibits natural killer cell activity
NGF	Stimulates cytokine release from T cells