REVIEW ARTICLE

Dimorphic Modulation of Immunity: From Gender to Hormones

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Abstract

The open circuit system of immunity is composed of different cellular and non-cellular components. However, the components are seemingly limited in view of their multifaceted actions. Hence, the particularity and functional diversity of immune system lie in the mode of regulation of all of its components. There are different factors which regulate the proper function and modus operandi of several components of immune system. Among them, one most important factor is regulation through hormones. There are different classes of hormones, but in context of immune system, hormones are immune-enhancing, immune-inhibitory, or immune-neutral. In-depth studies have shown that response of immune system varies with hormones of different kinds. It depends on the context (*in vivo* and *in vitro*), nature of hormone (steroid, proteinaceous, peptide, amino acid, and amino acid derivative), body condition (healthy vs. under pathological/clinical), and their behavior when in combination with other hormones and in contact with cellular and non-cellular components of immune system. It is notable that males and females of any animal differ physiologically and one of the reasons behind different physiology is involvement of hormones. Thus, it is a matter of investigation how gender-wise differentiation exists at immunological level. Till date, very little is known in this aspect and in-depth molecular studies are on the way to explore out the reason. This review, however, in brief, encompasses the dimorphism of immunity and immune response in terms of gender under hormonal regulation.

Key words: Dimorphism, gender, hormone, immunity

INTRODUCTION

The immune system is composed of many interdependent cell types that collectively protect the body from bacterial, parasitic, fungal, and viral infections and from the growth of tumor cells. Many of these cell types have specialized functions. The cells of the immune system can engulf bacteria, kill parasites or tumor cells, or kill viral-infected cells. Often, these cells depend on the T helper subset for activation signals in the form of secretions formally known as cytokines, lymphokines, or more specifically interleukins (IL).

Immunity is divided into two parts determined by the speed and specificity of the reaction. These are named as *innate* and *adaptive responses*, although, in practice, there is much interaction between them. The term innate immunity is sometimes used to include physical, chemical, and microbiological barriers but more usually encompasses the elements of the immune system (neutrophils, monocytes, macrophages, complement, cytokines, and acute phase proteins) which provide immediate host defense. The highly conserved nature of the response, which is seen in even the simplest animals, confirms its importance in survival.[1] Adaptive immunity is the hallmark of the immune system of higher animals. This response consists of antigen-specific reactions through T lymphocytes and B lymphocytes. Whereas the innate response is rapid but sometimes damages normal tissues through lack of specificity, the adaptive response is precise but takes several days or weeks to develop. The adaptive response has memory so that subsequent exposure leads to a more vigorous and rapid response, but this is not immediate.[2] The basic architecture of the immune system can be depicted as follows [Figure 1].

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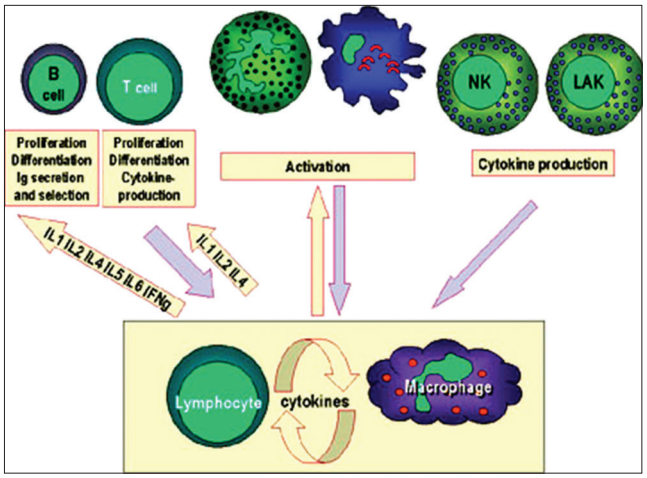

Figure 1: Different components of immune system - Photo courtesy: Nature Reviews Immunology, 2009[3]

Thus, from the above-mentioned information, it is clear that immune system which plays a most vital role in physiology and survival is composed of very small number of components (cellular or non-cellular). Hence, the functional diversity of this system lies in its types of factors regulating its function.

FACTORS REGULATING IMMUNE MODULATION

Effect of sex and sexual dimorphism in immune function

Immune responses are sexually dimorphic, both in type and magnitude. Two general systems of immunity to infectious agents have been selected during evolution - innate (natural) immunity and acquired (adaptive or specific) immunity. The innate immune system uses proteins encoding the germline (on macrophages, mast cells, and natural killer cells) to recognize the conserved products of infectious non-self (i.e., microbial pathogens) but not non-infectious self, i.e., host proteins.[4] Sex differences in mortality and immune competence are well documented in humans. Women in most of the societies not only have longer lifespans but also they are more resilient against infectious and some non-infectious diseases such as cancer.[5] This, however, comes at the price of women being more susceptible to autoimmune diseases.[6] These effects are commonly attributed to sexual differences in endocrinology.

The phenomenon of higher female immune competence is not only restricted to humans but also has been found in many vertebrates.[7] In their landmark paper, Folstad and Karter developed the idea of hormones driving sexual dimorphism in vertebrates and applied this to Hamilton and Zuk[8] idea that sexually selected ornament traits are dependent on health and vigor and therefore provide honest signals of genetic resistance.

Folstad and Karter's[7] "immune competence handicap hypothesis" assumes that testosterone suppresses immune function. In a nutshell, only males that are highly immune competent can handle the high testosterone titers that are needed to fully express their ornaments. This would result in a strong correlation between ornaments and immune competence (as an indicator of good genes), and hence, male ornaments would be honest traits. This elegant concept provides an explanation for how parasite-mediated sexual selection by Hamilton and Zuk[7] could work.

The assumption that testosterone is immune suppressive is debatable. While a great number of studies show a correlation between immunity and testosterone levels,[9] the experimental evidence is scant. A recent meta-analysis investigating the effects of testosterone on behavior and immunity did not find consistent support for the assumption that testosterone suppresses immunity.[10] Finally, many species of insect display female-biased sexual dimorphism in immunity,[11] yet insects are devoid of sex-specific hormones. Given that many of these species also show a positive correlation between ornament traits and immunity,[12] this calls into question the necessity of invoking an "immune competence handicap" for the expression of ornaments.

POSSIBLE HYPOTHESIS BEHIND SEXUAL DIMORPHISM

The physiological basis for the sexual dimorphism in immune function is not well understood. Sex differences in morphology, physiology, and behavior are usually mediated by sex steroid hormones.[13] Hormones may alter immunologic factors and responses, including antigen expression and presentation, and cytokine production, as well as the expression of apoptotic factors and cell death.[14] The modulatory actions of sex steroid hormones may be directly mediated through receptors on immune cells. In mice, the presence of estrogen receptors on various immune cells has been demonstrated, as well as the presence of androgen receptors on T- and B-cells.[15] These sex differences have been attributed in part to the modulatory actions of sex steroid hormones directly on immune cells.[15-17] Gonadal hormones may also influence immunological factors and responses through interactions with antigen expression and presentation, cytokine production, and the induction of apoptotic factors.[14,18,19] Importantly, social and environmental factors[19] may significantly modulate both gonadal hormone release and hormonal influences on immune responses. Sex steroid hormones also influence the immune response in part through the thymus in rodents and the bursa of Fabricius in birds through specific androgen and estrogen binding sites.[17] Early work investigating the effects of sex hormones *in vitro* on isolated leukocytes revealed no correlation between sex steroid concentrations and immune regulation.[20] Exogenous estradiol, however, stimulates adhesion molecules and their receptors on immune cells and accessory cells.[21] Estradiol also has immune-enhancing effects on antibody production

in vivo, whereas testosterone has immunosuppressive effects on B- and T-cell differentiation, as well as macrophage activation in rats and mice.[22] In birds, exogenous testosterone implants depress antibody production and delayed-type hypersensitivity (DTH) to an antigen challenges.[23] Although estradiol treatment has immune enhancing effects on humoral immunity, both cell-mediated immunity and natural killer cell activity are depressed following estradiol treatment in rats and mice.[24-26] Immune function varies according to the reproductive status as well. Male deer often have higher parasite load during the breeding season concomitant with high testosterone concentrations and exaggerated secondary sexual characteristics such as large antlers.[27]

Sexual dimorphism in human immune function arises during childhood, but it is not clear whether the molecular and cellular mechanisms involved are the same as those involved in the sexual differentiation of the brain. In all mammals that have been studied, a female phenotype unfolds during development in the absence of the androgenic products of the testes. During embryogenesis, the testes develop only after transcription of a gene on the Y chromosome, which encodes the testes determining factor. Early androgen secretions by the testes act to masculine and defeminize the circuitry of the male brain. This organizational action of androgen sets the stage for the post-pubertal activated effect of sex steroids. A number of genetic anomalies, e.g., testicular feminization syndrome or environmental perturbations, e.g., maternal stressors and drugs are known to interrupt the actions of androgens and consequently the process of masculinization of the brain. Sexual dimorphism in the adult rodent or primate brain is evident even in the absence of sex steroids.[28] For example, male rats castrated in adulthood are more sensitive to exogenous androgen as measured by behavioral tests and are less likely to respond with lordosis to estrogen treatment than gonadectomized females. This dimorphism can be abolished if castration occurs before the perinatal androgen surge that organizes the central nervous system (CNS) or if females are treated with sex steroids early in development. Therefore, the exposure to secretions from the testes early in life has a permanent effect on the CNS. What evidence is there that a similar organizational action of androgen occurs in the tissues and cells of the developing immune system?

DIMORPHISM IN HUMORAL AND CELLULAR IMMUNITY

A number of studies in various species, including humans, describe dimorphism in both humoral and cellular responses. Women have higher plasma IgM levels than men;[29] this difference becomes most significant at the time of puberty and is demonstrable in both African-American and Fair populations.[30] Levels of serum IgG have been found to be higher in Dark American women than in Black American men, but no such gender difference in IgG levels is observed in the White population.[30] In animal studies, females show more vigorous antibody responses to exogenous antigens.[31] Thymocytes and lymphocytes from normal female mice respond more vigorously to exogenous and allogeneic antigens than do cells from male mice. Parallel studies of T cell function in humans are lacking; however, quantitative differences in relative numbers of functional T cells have been related to gender.[32,33] Higher CD4:CD8 ratios are generally seen in females and hypogonadal males[34] due to relatively lower numbers of circulating CD8 T cells. Specifically, cell-mediated immune responses differ between males and females. T-cells, in particular helper T-cells (Th cells), are functionally and phenotypically heterogeneous and can be differentiated based on the cytokines they release. Reliance on subsets of Th cells (i.e., Th1 or Th2 cells) to overcome infection differs between males and females with females exhibiting higher Th2 responses (i.e., higher IL [IL-4, IL-5, IL-6, and IL-10 production] than males.[35] Female rodents also have higher mitogen-stimulated lymphocyte proliferation and increased immunological intolerance to foreign substances than males.[36] The thymus in female mice is larger, and castration of young males leads to an increase in weight of the thymus and secondary immune organs[37] and to an expansion of bone-marrow B cells.[38] In the hamster, sexual dimorphism in the primary and secondary antibody response arises around puberty and is correlated with larger relative spleen weights in females.[39] Sexual dimorphism can be demonstrated in many aspects of immune function. For example, in the mouse, complement is particularly interesting because there is not only a quantitative but also a qualitative difference. Electrophoresis of plasma from the male reveals molecular forms of complement C5 and BF which are absent in females. *In vitro* studies of Fisher-344 rat macrophages also show that cells derived from females produce larger amounts of prostaglandin E and thromboxane B_2 than those from males.[40] Women develop higher titers of antibodies in response to immunization, reject transplanted tissues more quickly, are more susceptible to allergies, and live longer than men. They also experience elevated frequencies of many autoimmune diseases with systemic lupus erythematosus (SLE) and Sjogren's syndrome 9 times more common in females. Autoimmune nephropathies and Type 1 diabetes, on the other hand, are slightly more common in males. Interestingly, SLE can occur prepubertally, but it is not clear if the sex ratio favors girls at this stage; however, some parameters of immune function are sexually dimorphic even in childhood. For example, Butterworth *et al*.[29] showed that differences in immunoglobulin-M (IgM) levels begin in mid-childhood with girls having higher levels. A whole host of sex differences such as these has prompted extensive research on sex-steroid regulation of immune response and autoimmunity in animal models. The earlier studies have been well reviewed by Schuurs and Verheul.[41]

Neuroendocrine regulation of immune function

The immune system is affected by many external and internal factors such as this hormone system. Recent studies are only

now showing us how complicated the relationship is between our immune system and hormone system. Good example is a recent study, showing that we respond to infection with complex bidirectional communication between this immune system and this neuroendocrine system.[42] Cells of the immune system contain receptors for neuroendocrine hormones, i.e., they receive messages. Immune system then sends out the troops against invaders. It also forms amino acid chains called peptides. These peptides are similar to the hormones produced by neuroendocrine system. They appear to function as immune regulators as well as information carriers from the immune system back to the neuroendocrine system. Another recent study showed the importance of this communication. This study investigated the role of the pineal gland and its principal hormone and melatonin on the immune system, through its control of the release of cytokines.[43] The study was carried out on 31 cancer patients with advanced solid tumors who had failed to respond to chemotherapy and radiotherapy. The patients received melatonin for 3 months. 39% of patients achieved disease stabilization with no further growth of either the primary or secondary tumors. The researchers concluded that the pineal gland and melatonin, in particular, modulate immune function in cancer patients by activating the cytokine system which then exerts growth-inhibitory properties over a wide range of tumor cell types [Figure 2].

ROLE OF DIFFERENT HORMONES IN SEX-DEPENDENT IMMUNE RESPONSE

Darwin[46] noted that frequently males are shortlived than female cospecifics; this observation is particularly true among polygynous species.[47] Although there is evidence that differential environmental and social interactions can account for some of the sex differences in mortality, it is clear that males and females differ in immune function. For example, when male and female mice are maintained in germ-free environments, the sex difference in longevity vanishes. Sex differences have been reported for several immune indices.[18,25,36,41] In general, sexually mature females seem to have higher immune activity than male conspecifics. For example, females of many species, including humans, have higher circulating Ig levels than male cospecifics.[47,48] Females also mount higher antibody responses after an immunological challenge than males.[41] Macrophages from adult female rats produce more IL-1 than pre-pubertal females or adult males;[49] ovariectomy reduces macrophage IL-1 production in female rats, and estrogen replacement therapy reverses this reduction.[50] Cell-mediated immunity has been reported to be both lower[51] and higher[52,53] in female mammals as compared to males [Table 1]. However, virtually all studies indicate that females exhibit higher resistance to tumors and parasites than males.[18,54] Many sex differences in immune function appear to be organized early in development and are activated at the time of puberty,[18] although some appear only to be activated by peripubertal increases in sex steroid levels.[41]

In context of diseases females are more resistant than males.[18,36,41] Among humans, for example, females are less likely than males to contract bacterial meningitis, bacterial septicemia, dysentery, gonorrhea, meningitis, pneumonia, Legionnaires' disease, hepatitis B, rabies, syphilis, tetanus, typhoid, and yellow fever.[36] The disadvantages of such superior immunological function and resistance to disease among females include enhanced proclivity for developing autoimmune disease.[18,36,41] Women are more likely than men to suffer from SLE (9:1), Sjogren's syndrome (10:1), rheumatoid arthritis (3:l–7:1), multiple sclerosis (2:I), Graves' disease, thyroiditis, and certain forms of diabetes. [18,36,41] Animal models for many human autoimmune diseases exist, and hormonal manipulations in these animal models have indicated the involvement of sex steroid hormones in their expression.[55] Furthermore, natural hormonal changes in humans (e.g., pregnancy and menopause) have an effect on immune function and some diseases. In general, estrogens are immune stimulatory, androgens are immune compromising, and progestins can be either stimulatory or suppressive of immune function.

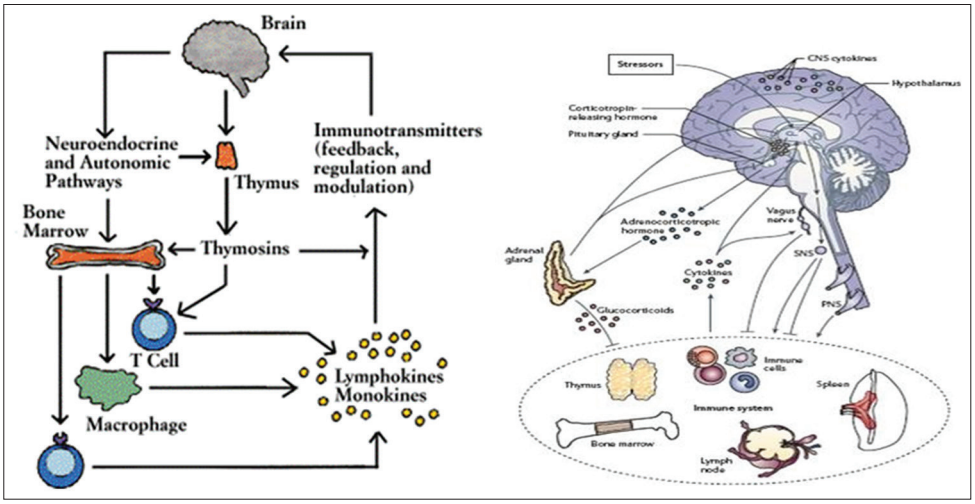

Figure 2: Neuroendocrine-immune interactions - Photo Courtesy www.google.co.in[44]

Table 1: Neuroendocrine factors and their effects on immune function

Hormone	Cytokine/immune function
α-endorphin	Inhibits Ig production
α-MSH	Suppresses DTH and inhibits IL-1 and IL-2 production through inhibition of NF-κB
Acetylcholine	Stimulates T and NK cells, increases IFN-γ production ACTH, inhibits IFN-γ production and Ig production, and blocks macrophage activation by IFN-γ
Adrenaline	Inhibits IL-1 and IL-2 production
Angiotensin 2	Enhances IFN- γ production
β-endorphin	Enhances IFN-γ production and NK-cell-mediated cytotoxicity and inhibits T-cell proliferation
cAMP	Enhances IL-4 and IL-5 production and inhibits IL-2 production
Calcitonin gene-related peptide	Increases T-cell adhesion and stimulates IL-2, IL-4, and IFN-γ production
Catecholamines	Enhance Ig production. Decrease the number of T and NK cells in the peripheral circulation and inhibit NK cells
Cortisol	Inhibits IFN-γ, IL-2, IL-6, and TNF-α, enhances IL-4 and TGF-α production, and enhances immune cell expression of IL-1, IL-2, IL-6, and IFN-γ receptors
CRH	Activates macrophages and inhibits IL-1 and IL-6 production
DHEAS	Enhances IFN-γ production and T-cell proliferation
Growth hormone	Activates macrophages and enhances H_2O_2 production
Gonadotropin-releasing hormone	Increases IL-2R expression, T- and B-cell proliferation, and serum Ig
Histamine	Inhibits IL-12, TNF-α, and IFN-γ and enhances IL-10 production
Inhibin	Inhibits IFN-γ production
IGF1 and IGF2	Enhance PBMC proliferation
LH	Enhances IL-2-stimulated T-cell proliferation
Macrophage inhibitory factor	Blocks glucocorticoid inhibition of T-cell proliferation and cytokine production
Melatonin	Enhances IL-1, IL-2, IL-6, and IFN-∃© production
Met-enkephalin	Enhances antigen-specific proliferation
Nerve growth factor	Enhances B cell proliferation, IL-6 production, IL-2 receptor expression, and Ig-G4 synthesis
Neuropeptide Y	Increases T-cell adhesion and stimulates IL-2, IL-4, and IFN-γ
Estrogen	Enhances T-cell proliferation and activity IFN-γ gene promoter
Oxytocin	Enhances IFN-γ production
PGE2	Inhibits IL-2 production
Progesterone	Enhances IL-4 production and CD30 expression
Prolactin	Enhances T-cell proliferation, IFN-γ, IL-2 receptor expression, and macrophage function
Serotonin	Inhibits T-cell proliferation and IFN-γ-induced HLA class II expression and enhances NK cytotoxicity
Somatostatin	Inhibits T-cell proliferation and IFN-γ production
Substance P	Enhances T-cell proliferation and IL-1, IL-6, TNF-α, and IFN-γ production and macrophage action
Testosterone	Enhances IL-10 production
TSH	Enhances IL-2, GM-CSF, and Ig production
Thyroxine	Activates T cells
Vitamin D3	Inhibits IL-2 and IFN-γ and enhances IL-4 production
Vasopressin	Enhances IFN-γ production
VIP	Inhibits T-cell proliferation and IL-12 and enhances IL-5 and cAMP production

Source: Nikolai Petrovsky, Toward a unified model of neuroendocrine-immune interaction, Immunology and Cell Biology (2001) 79, 350–357.[45]. ACTH: Adrenocorticotrophic hormone, CRH: Corticotrophin-releasing hormone, DHEAS: Dehydroepiandrosterone sulfate, DTH: Delayed-type hypersensitivity, IGF: Insulin-like growth factor, LH: Luteinizing hormone, MSH: Melanocyte-stimulating hormone, NF-κB: Nuclear factor-κB, TSH: Thyroid-stimulating hormone, VIP: Vasoactive intestinal polypeptide, TNF: Tumor necrosis factor, G-CSF: Granulocyte colony-stimulating factor

ROLE OF GONADAL STEROIDS IN IMMUNE MODULATION

Steroidogenesis is the biological process by which steroids are generated from cholesterol and transformed into other steroids. Both clinical and experimental evidence support the hypothesis that gonadal steroids regulate immune function. This conclusion is based on the following observations: (i) A sexual dimorphism exists in the immune response; (ii) the immune response is altered by gonadectomy and sex steroid hormone replacement; (iii) the immune response is altered during pregnancy when the amount of sex steroid hormone is increased; and (iv) the organs responsible for the immune response contain specific receptors for gonadal steroids.

ROLE OF ANDROGEN

Testosterone generally suppresses immune function. Castration of adult male rodents results in increased Ig levels, increased humoral and cell-mediated immunity, and increased lymphatic organ size, including thymic, splenic, and lymph nodal masses.[41] Castration of male rodents leads to similar immune responses, but they are not equivalent to those females; this suggests that some of the sex difference in immune function is organized before puberty. Treatment of adult castrated males with physiological doses of testosterone restore (i.e., depress) immune function to pre-castration levels.[18,41]

Testosterone replacement therapy of castrated male rats and mice significantly suppressed thymic mass, humoral and cell-mediated immunity.[36,41] Androgen receptors have been identified in thymic tissues, particularly in the epithelial, lymphatic portion of the thymus.[25,56] Androgenic effects on lymphocytes may be in direct or through aromatization of androgens to estrogens because no androgen receptors have been found on circulating lymphocytes.[25] It is apparent that the immune and reproductive systems are intimately interconnected and that androgens are important components of these interactions. Indeed, the immune system can be modulated by androgens in some cases; conversely, activation of the immune system, particularly the innate arm, is associated with suppression of the reproductive neuroendocrine axis.[57] Further, in domestic fowl, birds selected for strong antibody responses have smaller combs and sexually selected traits that are testosterone dependent and lower testosterone titers.[58] Conversely, chickens infected with an intestinal parasite exhibited similar concentrations of testosterone and similar-sized combs as uninfected birds.[59] As evidenced by these studies, trade-offs between reproduction and immune function may be mediated directly through communication between the reproductive and immune systems in certain contexts,[60,61] although these interactions tend to be complex. The apparent immunosuppressive effects of androgens may sometimes be due to glucocorticoids,[62,63] at least in certain experimental contexts. For example, captive dark-eyed juncos (*Junco hyemalis*) implanted with testosterone had reduced PHA responses when compared with those without implants. This effect could not be attributed directly to testosterone, as birds with implants also had higher circulating Corticosterone.[64] Similarly, house sparrows implanted with testosterone had decreased antibody response but increased corticosterone concentrations.

EFFECTS OF ANDROGENS ON CELLULAR AND HUMORAL IMMUNITY

Several studies in both animals and humans have been performed in an attempt to understand the influence of sex steroids on the immune system. Androgens exert considerable effects on the size and composition of the thymus. Removal of androgens by castration resulted in thymic enlargement even in old rats, and androgen replacement reversed this effect.[65] In one study, testosterone replacement in castrated male mice caused thymic regression, with a shift toward the expression of mature thymocytes and predominance of the suppressor/cytotoxic CD4-CD8+ phenotype over the helper CD4+ CD8- phenotype.[66] Mechanisms of androgen-induced thymus involution are incompletely understood but decreased cell proliferation; changes in cell trafficking and increased apoptosis are some of the possible mechanisms involved. The role of apoptosis was suggested by one study from Olsen *et al*.,[67] in which a single dose of testosterone markedly decreased thymic size within hours in castrated mice; increased DNA fragmentation was shown, suggesting thymocyte apoptosis. Recently, it has been shown that testosterone specifically targets double positive (CD8+CD4+) thymocytes for apoptosis through upgrading tumor necrosis factor-α (TNF-α) production.[68] On the other hand, documentation of classical AR expression in peripheral T cells has not been reported, but the net effect of androgen action (direct or indirect) seems to be an enhanced suppressor effect.[15] The number of pre-B cells in bone marrow and mature peripheral B cells increases in male mice after castration.[69] It has been reported that treatment of mice with dihydrotestosterone (a non-aromatized androgen) suppressed the expansion of lineage precursors (IL-7 responsive precursors) when added to short-term cocultures of lymphocytes and stromal cells.[70,71] There are conflicting data concerning the effects of castration and androgens on peripheral B cells. CD5+ cell subsets have been implicated as an important source of auto-antibodies. An early study showed that this B cell subset did not expand in spleens of castrated male mice, whereas estrogen treatment in female mice augmented the CD5+ cell subset activity,[55] suggesting the greater importance of estrogen (rather than the absence of androgen) in the activation of CD5+ cell subsets. In a recent study, castration in male mice was shown to selectively increase splenic cellularity and the number of peripheral blood lymphocytes due to newly emigrated immature B cells. It was concluded that a number of B cells in male mice were controlled by physiological levels of androgen.[72]

ESTROGEN

In contrast to the pattern of androgen receptor localization, estrogen receptors have been localized in the cytosol of circulating lymphocytes,[16,18,73] CD8+ cells,[74,75] and thymic cells.[73,76] Physiological treatment of estrogen, or the estrogen receptor antagonists, tamoxifen and FC1157a, enhances pokeweed mitogen-induced Ig synthesis of B lymphocytes.[77]

Treatment of intact male or gonadectomized male or female mice and rats with physiological or supra-physiological doses of estrogens increases antibody responses to a variety of T-dependent and T-independent antigens.[51,78] Cyclic exposures to pharmacological doses of estrogens are more effective in boosting antibody formation than chronic estrogen exposure.[41] Pharmacological doses of estrogens also suppress cell-mediated immunity.[18,79] Tamoxifen inhibits the effects of estrogens on antibody formation and cell-mediated immunity.[80,81] Taken together, the effects of physiological doses of estrogen appear to enhance immune function.

EFFECTS OF ESTROGENS ON CELLULAR AND HUMORAL IMMUNITY

Estrogen treatment has been shown to cause significant thymic atrophy and to decrease the number of thymocytes in mice.[82] In a study with ovariectomized female rats, ovariectomy increased thymic size and had a profound effect on the thymocyte profile, leading to an increase in the CD4+CD8+ immature cells, with a decrease in the relative proportion of the mature cells, which was opposed by treatment with physiological doses of estradiol-17β.[83] Estrogen also stimulates CD4+CD8- cells and can activate an extrathymic pathway of autoreactive T-cell differentiation in the liver.[82,84] Several studies have established that estrogen is a potent inhibitor of stromal cell-dependent B cell lymphopoiesis *in vitro*. In bone marrow, all the precursors beyond the early pro-B cell stage are affected by estrogen.[85,86] In a recent study, the same authors observed a dramatic reduction in B cell lineage differentiation and expansion when estrogen was added to stromal-free cultures, suggesting a direct effect of estrogen on early pro-B cells.[87] Estrogen also affects peripheral B cells and humoral immunity. Estrogen treatment in normal male or female mice increased the number of antibody-producing cells and the levels of circulating auto-antibodies against double-stranded DNA (dsDNA) without any increase in B cell count.[88] In another study, using human peripheral blood mononuclear cells, estrogen treatment was showed to enhance Ig production, partially by increasing IL-10 production.[89] In summary, androgens and estrogen are potent immune modulators. Sex steroids act as negative regulators in both the thymus and bone marrow, but androgens and estrogen tend to affect different subsets of immune cells. In general, androgens seem to inhibit immune activity, while estrogen seems to have a more powerful effect on immune cells and to stimulate immune activity.

ROLE OF STRESS HORMONE (GLUCOCORTICOID) IN IMMUNE MODULATION

Glucocorticoids are the end product, primary effectors, and principal negative regulators of an important neuroendocrine axis (hypothalamus–pituitary–adrenal [HPA] axis). Originally described for their role in energy mobilization, glucocorticoids are now recognized as powerful mediators of many physiological processes including reproduction and immune activity. Unlike other hormones, glucocorticoids tend to suppress both reproduction and immune function. The effects of glucocorticoids on immune function and susceptibility to infection are most well understood in mammalian species. High circulating corticosterone concentrations suppress innate (i.e., natural killer cell activity), cell-mediated (i.e., cytokine production), and humoral (i.e., antibody production) immune responses in laboratory rats and mice.[90,91] Furthermore, adrenalectomy increases lymphoid tissue mass and B cell activity in mice.[92] Laboratory studies in rodents have demonstrated that basal corticosterone concentrations are higher among females and rise more rapidly in females than males following exposure to stressors.[93,94] Males and females often differ in the types of stressors they encounter, especially during the breeding season.[95,96] Thus, exposure to stressors may influence sex differences in immune function and subsequent resistance to infection.[27] This observation has led to the principles that elevated glucocorticoids promote physiological and behavioral responses that (i) favor immediate survival at the expense of other processes (i.e., the emergency life history stage hypothesis[97] and (ii) maintain homeostasis in the face of environmental changes (i.e., allostasis[98]). Interaction between glucocorticoids and the immune system is complex and bidirectional. Stressor-induced elevated glucocorticoid concentrations can modulate immune activity; however, activation of the immune system can also drive the production of glucocorticoids.[57,99] Since glucocorticoids tend to suppress inflammation but be induced by pro-inflammatory stimuli, they have been conceptualized as "brakes" on the immune system, having evolved to prevent runaway inflammation and promote fine-tuning of the immune response.[100] A wealth of information demonstrates how glucocorticoids suppress immune function,[99] which led to the conjecture that glucocorticoids are largely responsible for decrements in immune activity in free-living animals in winter.[101] Now, there is compelling evidence that, in certain contexts, glucocorticoids can enhance aspects of immune function. In many cases, immune suppression may be immune redistribution in disguise.[102] From an adaptive perspective, one might predict that animals would enhance immune function in parts of the body at times when injury is probable, such as during a territorial dispute or failed predation event. Recent data in mice and rats support part of this prediction; in response to acute stressors, circulating leukocytes do not die, but instead they leave the bloodstream and move into peripheral tissues (skin, gut, and lymph nodes). In the absence

of injury or infection, these cells return to the general circulation quickly.[103] One of the best examples of these stress-induced immune redistributions comes from work on DTH. The DTH response is characterized by T-cell-mediated trafficking of immune cells into the skin.[104] These stress-induced alterations in the DTH response were directly mediated by corticosterone. Photoperiod affects the character of these stress-induced immunological redistributions, suggesting that these hormones probably influence seasonal changes in immune activity in wild animals. Siberian hamsters acutely stressed before immune challenge had elevated DTH responses, and this response was significantly augmented in short- versus long-day animals.[105] This enhancement in skin immune function was associated with an enhanced glucocorticoid response and expedited movement of leukocytes out of the blood during restraint stress in short- versus long-day-housed hamsters.[105] As with photoperiod, the latitude of origin can also influence corticosteroid effects on the immune system. Tropical-dwelling, but not temperate, house sparrows failed to show immune suppression in response to chronically elevated corticosterone.[106]

ROLE OF METABOLIC HORMONE (THYROXIN) IN IMMUNE MODULATION

Thyroid hormones are basically known to regulate basal metabolic rate of the body. However, the immune modulatory role of this hormone is least known and in need to be elucidated. However, reports suggest that it is helpful in differentiation, growth, metamorphosis, and metabolism[107] and play a prominent and critical role in the regulation of reproduction.[108] Some previous reports suggest that thyroxin (T4) caused thymus enlargement and increased in umber of peripheral lymphocyte.[109] However, thyroidectomy resulted in hypoplasia of lymphoid organs[110] as thyroid hormones are reported to increase the nucleated cells in spleen, thus improving the immune status of an immune compromised animal to the threshold level.[111] Some of the reports are contradictory to the previous citations where Weetman *et al*.[112] reported that, under *in vivo* and *in vitro* conditions, thyroxin has no role in immune modulation. Another report of Gupta and Thapliyal[113] suggests that thyroxin in immune inhibitor in nature. However, most of the reports are mainly from birds but not from mammals. Some partial report[114] suggests that thyroid hormone functions may be modulated by melatonin and it can also affect the lymphoid organ function by modulating pineal-thyroid axis.[108] However, the exact role of thyroid hormone function in the modulation of immunity is till date controversial, partial, and in need to be explored out.

NEUROENDOCRINE IMMUNE CROSS TALK

A good example of neuroendocrine-immune cross talk is the role of prolactin in regulating T-cell cytokine production. Prolactin shares target transcription factors including interferon regulatory factor-1 with IL-2.[115] Prolactin receptors are expressed on T and NK cells, and prolactin increases IL-2-stimulated NK-cell IFN-γ production.[115] This is an example of an increasingly recognized phenomena whereby simultaneous signaling through hormone and cytokine receptors on T cells result in downstream interaction of receptor signaling pathways and result in T-cell behavior that may not be predicted on the basis of signaling through individual receptors. T cells express over 20 neuroendocrine receptors and at least as many cytokine receptors, and thus the level of complexity of intracellular cross talk must be immense. The diversity of T-cell behavior under different conditions is likely, therefore, to have its origins in this receptor cross talk involving neuroendocrine and cytokine receptors. Thus, reductionist experiments examining the role of individual factors in T-cell subset differentiation may be less important than an examination of the overall cytokine and hormonal milieu *in vivo* at the time of T-cell activation in understanding T-cell subset differentiation.

CYTOKINE REGULATION OF NEUROENDOCRINE FUNCTION

In keeping with the bidirectional nature of the neuroendocrine and immune pathways, cytokines also influence neuroendocrine function. This was highlighted by the early finding that corticosterone levels are increased several fold during the primary immune response of rats to sheep red blood cells. Immune influences on neuroendocrine function are now known to be principally mediated by cytokines, receptors for which are widely expressed throughout the neuroendocrine system.

The first cytokines shown to have neuroendocrine effects were the interferons, administration of which increases steroidogenesis. Subsequently, IL-1, IL-2 or IL-6, IFN-γ, IFN-β, leukemia inhibitory factor, and TNF-α have been shown to elevate plasma adrenocorticotrophic hormone (ACTH) and glucocorticoid levels in both laboratory animals and humans.[116-118] Cytokines also regulate the secretion of non-HPA axis hormones. For example, IFN-γ, granulocyte colony-stimulating factor (G-CSF), and GM-CSF stimulate melatonin release by the pineal gland.[119] Potentially, this constitutes yet another positive feedback loop because melatonin itself enhances IFN-γ production.[120] Interferon-γ upregulates glucocorticoid receptor expression by macrophages, suggesting that the action of glucocorticoids on immune cells may be enhanced at times of immune system activation.[121]

Some cytokines may even cross-react with neuroendocrine receptors. For example, IL-2 has analgesic effects in both the central and peripheral nervous systems, and this may be mediated through interaction of the analgesic domain of IL-2 with the opioid receptor [Figure 3].

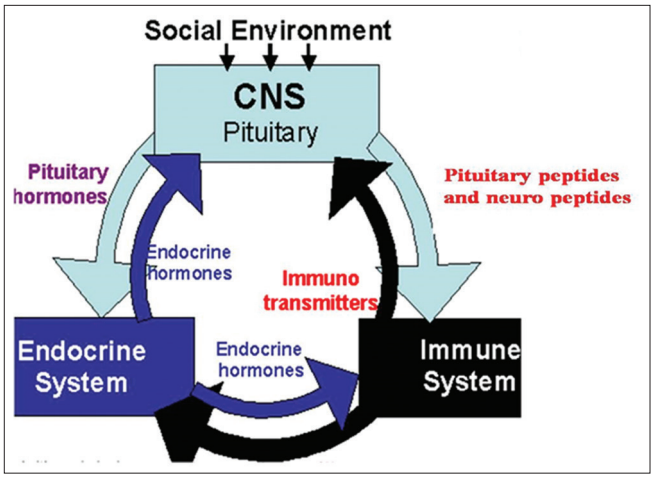

Figure 3: Influence of social factors affecting neuroendocrine and immune systems - Photo courtesy www.google.co.in[41]

EXPRESSION OF HORMONE BY IMMUNE CELLS

Lymphocytes express receptors for a wide variety of hormones, including cortisol, prolactin, GH, and melatonin. Immune cells are also capable themselves of expressing many hormones. Over 20 different neuroendocrine hormones and/or mRNA for hormones including ACTH, thyroid-stimulating hormone, GH, prolactin, and CRH are expressed by lymphocytes and/or monocytes.[122] For example, human PBMC expresses gonadotropin-releasing hormone (GnRH), GnRH receptor, and IL-2 receptor gamma-chain mRNA that are regulated by GnRH *in vitro*.[123] Thymus expressed glucocorticoid may even have a role in the regulation of antigen-specific T-cell development.[124]

CONCLUSION

From the brief review, we may conclude that there are gender-dependent variations of hormonal regulation of immunity irrespective of the fact that the hormone is immune-enhancing, immune-suppressive, or immune-neutral. However, in-depth molecular studies are warranted to get a holistic view.

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