Indo American Journal of Multidisciplinary Research and Review (IAJMRR)
ISSN: 2581 - 6292 / Impact Factor: 6.885 / Website: www.iajmrr.com

ANALYSIS IN THE ROLE OF SEX HORMONES IN FEMALES FIGHTING AGAINST INFECTIOUS DISEASE

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Cite This Article: Dr. Don J Scott Berin G, "Analysis in the Role of Sex Hormones in Females Fighting Against Infectious Disease", Indo American Journal of Multidisciplinary Research and Review, Volume 7, Issue 1, Page Number 14-19, 2023.

Abstract:

Sex hormones plays a critical regulatory role in the development and maintenance of immunity against infections in females. Its role in the regulation of antibody synthesis. Here the effect of estrogen on T cell-dependent (TD) and T cell-independent type 2 (TI-2) antibody responses. The results provide the first evidence that estrogen enhances the TD but not the TI- 2 response. Estrogen may have a direct impact on B and T cells by inducing rapid signaling events, such as Erk and AKT phosphorylation, cell-specific Ca2+ signal, and NFJB activation. These no transcriptional effects are mediated by classical estrogen receptors and partly by an as yet unidentified plasma membrane estrogen receptor. Such receptor- mediated rapid signals may modulate the T cell-dependent immune response.

Key Words: Sex Hormones, Estrogen, Immune System, T and B Cells Immunity, Corona Virus.

Introduction:

Sex hormones play an essential role in regulating immune response against corona kind of infection in females, through its interactions with the receptors on the immune cells which affects the production, maturation, differentiation, and ultimately the functioning of immune cells. Generally, estrogen stimulates the production of immunoglobulin's by plasma cells, and directly up regulates the expression of mediators of B cell survival, such as CD22, SHP-1, and Bcl-2 and impairs mediators of B cell apoptosis such as PD-1. On the other hand, estrogen exerts repressive effects on the innate immune, by increasing regulatory T cells (Tregs) frequency and number, controlling the expression of certain chemokine receptors in T cells, repressing monocytes and neutrophils to secrete proinflammatory cytokines in response to activating stimuli, or impairing natural killer (NK) cell cytotoxicity. Taken together, these findings suggest that estrogen signaling is important in establishing the balance of immunity and tolerance.

Abbreviations:

AEC 3	Amino-9-ethylcarbazole
[Ca2+]	Intracellular free Ca2+
CLSM	Confocal laser scanning microscopy
DCC-FCS	Dextran-coated charcoal-treated foetal calf serum
aE2	17a-Estradiol
bE2	17b-Estradiol
eNOS	Endothelial isoform of NO synthase
ERa	Nuclear estrogen receptor a
ERb	Nuclear estrogen receptor b
HRT	Hormone replacement therapy
KLH	Keyhole limpet hemocyanin
SHAM	Sham-operated
TD	T cell dependent
TI-2	T cell independent type

Immune System:

Immune response is divided into two categories: nonspecific and specific. Nonspecific immune response is the innate or natural immune response that acts as the first line of defense against infections and recognizes structures like microbes. The components of nonspecific immune response are monocytes, macrophages, natural killer (NK) cells, dendritic cells, and granulocytes: neutrophils, eosinophils, and basophils.These cells attack microbes by phagocytosing them (neutrophils, monocytes, and macrophages), by lysis of infected cells (NK cells), or by producing cytokines to enhance nonspecific immune and specific immune responses.

Dendriticcells together with monocytes and macrophages act as antigen presenting cells (APCs). They take up foreign antigens(including viruses or pathogens), process them, and present antigen peptides on their surface for specific immune system mainly helper T lymphocytes .The specific immune response is divided into two types, that is, cell mediated and humoral immune response. Cell mediated immune response does not include antibodies but active immune cell population, namely, phagocytes, antigen specific T lymphocytes, and various cytokines, whereas humoral immune response is mediated by macromolecules found in extracellular fluid such as antibodies.

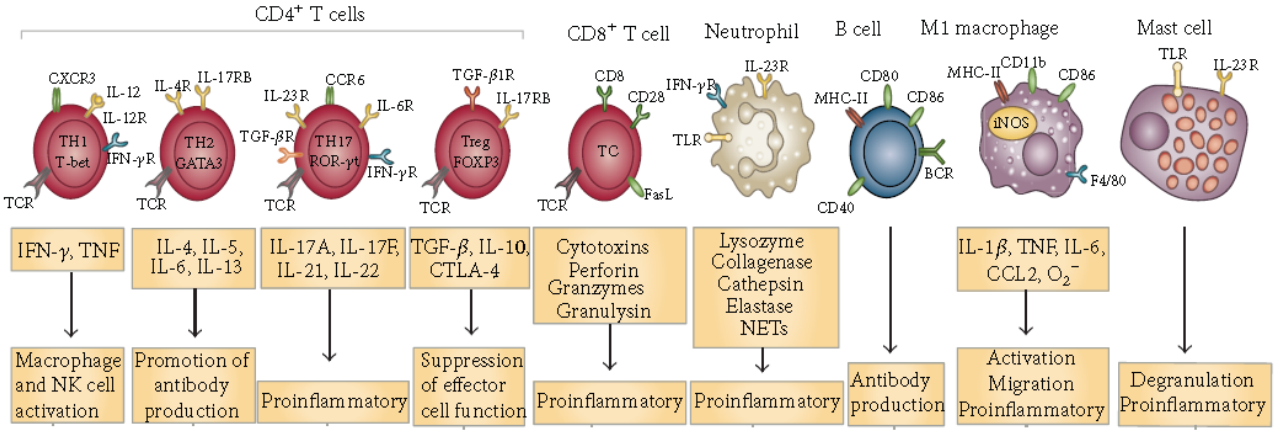
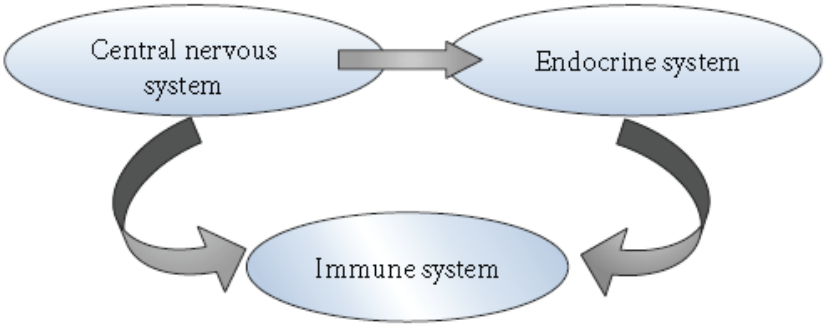


FIGURE 1: Cells and molecules of specific and nonspecific immune system [48, 49].

T lymphocyte population is divided into cytotoxic T lymphocytes (Tc cells) that kill foreign or infected cells and helper T lymphocytes (Th cells) that provide help to other immune cells by producing cytokines. These Th cells are further divided into subtypes, that is, the Th1 subset producing interferon (IFN)gamma that promotes cellular immune responses, the Th2subset producing mainly interleukin-4 (IL-4), IL-13, and IL-5to aid humoral immune responses, and the Th17 subset producing IL-17, which plays a crucial role in autoimmunity and allergen-specific immune responses. The third division of T lymphocytes is regulatory T cell (Treg) that is centre of immune regulation and is capable of suppressing both Th1-andTh2-mediated specific immune responses.



Sex Hormones:

Estrogen:

Estrogens are present in significant amounts in both men and women. They are present in significantly higher amounts in women after menarche (on set of menstrual periods at puberty) until menopause (cessation of menstrual periods after completion of reproductive age).The primary function of estrogens is development of female secondary sexual characteristics. These include breasts, endometrium, regulation of the menstrual cycle etc. In males estrogen helps in maturation of the sperm and maintenance of a healthy libido.

Physical Functions:

Estrogen is responsible for development of the female body and the secondary sexual characters. It helps in major role in height increase in females during puberty, accelerates burning of body fat and reduces muscle bulk.It also stimulates growth of the inner lining of the uterus (endometrium)during the menstrual cycle, increases uterine growth, improves lubrication ofthe vagina, and thickens the vaginal wall while increasing blood vessels to the skin.

Effects on Various Biochemical Parameters:

Estrogens reduce bone resorption and increase bone formation. They help in protein synthesis, increase hepatic production of binding proteins, coagulation proteins (factors II, VII, IX, X, plasminogen). Estrogens increase platelet adhesiveness and reduce antithrombin III. Estrogens increase good cholesterol (HDL) and also increase triglycerides. They decrease LDL and promote fat deposition. On fluids and electrolytes estrogens cause salt (sodium) and water retention. In the gastrointestinal tract they reduce bowel motility and increase in the gastrointestinal tract they reduce bowel motility and increase cholesterol in bile. They also improve lung functions.

Effects on Hormones:

Estrogens increase cortisol and Sex hormone binding globulin. Estrogens increase melanin and pheomelanin and reduce eumelanin.

Estrogens and Cancer:

Estrogens help in the growth and maintenance of hormone sensitive breast cancers.

Estrogen and Libido:

Sexual desire is dependent on androgen levels rather than estrogen levels. Estrogen and development of the fetus. Estrogen helps in causing physical differentiation of the fetus to either malesor females as per their genetic code. While androgens like testosterone lead to masculinizing the fetus, estrogen feminizes the fetus. Prenatal androgens act on behavior and other tissues, with the possible exception of effects on bone via androgen receptors.

Estrogen and Mental Health:

Estrogen is considered to play a significant role in women's mental health. Sudden decrease in blood levels of estrogen and periods of sustained estrogen low levels correlate with significant mood lowering. After childbirth, nearing menopause and after menopause low levels of estrogen can predispose to depression.

Estrogen and Skin:

For many years it has been recognized that estrogens are important in the maintenance of human skin. They improve collagen content and quality, increase skin thickness and improve blood supply to the skin. Estrogens act via estrogen receptors on human skin. The number of estrogen receptors varies in different parts of the body. Highest receptor levels are seen on the facial skin and skin over thigh or breast.

Estrogen and Heart Disease:

Estrogen deficiency increases the risk of heart disease. Lack of estrogen is animpetus to atherosclerosis.

Estrogen Receptors on Immune Cells:

Estrogen helps the immune system by increasing the number of circulating immune cells. Sex hormones either helps proliferation/apoptosis of the cells or induce production of new cells from the bone marrow. Sex hormones are steroids that arelipophilic in nature which facilitate their diffusion through cell membrane. This makes the genetic material in the cell directly. Some biotechnologist and immunologist describes that nongenomic effects of steroid hormones which are regulated via membrane receptors for these hormones on immunocytes. Due to their lipophilic nature, sex steroids are able to alter membrane properties of immune cells by integrating into their membrane. This integration changes the function of immune cells. In different reference I used to find that intracellular estrogen receptors are present in T lymphocytes and B lymphocytes, dendritic cells, and monocytes, in humans. As established by various studies activated lymphocytes during pregnancy.

Transcription of a number of genes is regulated by steroid hormones by interacting with intracellular receptors, which are modular proteins, composed of a lig and binding domain, aDNA binding domain, and several transactivation functions distributed along the molecule. Regulation of gene expression by hormones involved an interaction of the DNA-bound receptors with transcription factors which was also studied to be mediated by co activators and co repressors. Depending on the nature of these interactions, the final outcome could be induction or repression of transcription.

Effect of hormones on the immune response has been shown due to their effect on differentiation and maturation of Immunocytes. Determination of the effect of antiestrogens on differentiation and maturation of dendritic cells was carried out by immunologist. The differentiation inhibitory effect of non steroidal anti estrogens (toremifene and tamoxifen) in the cultures of immature CD1apositiveDC in vitro from CD14-positive monocytes in the presence of interleukin-4 (IL-4) and granulocyte macrophage colony-stimulating factor. In the presence of antiestrogensthe cells lost CD14 expression but remained CD1a-negativeand have less dendritic processes than immature DC. Functionally, antiestrogen-treated cells were inferior to immature DC in inducing proliferation of allogeneic T cells and inproducing IL-12 p70 protein after CD40 ligation.

The expression of the costimulatory molecules CD80 and CD86 was differentially regulated by antiestrogens during DC differentiation. Antiestrogens were also able to inhibit the terminal maturation of DC. While looking for the changes in the immune system during pregnancy an increased progesterone sensitivity of lymphocytes was observed which was due to activation-induced appearance of progesterone binding sites in the lymphocytes. Following recognition of fetus derived antigens γ/δ TCR+ cells developed progesterone receptors. Progesterone binding resulted in the synthesis of a mediator protein named the progesterone-induced blocking factor (PIBF). PIBF by acting on the phospholipase A2 enzyme interfered with arachidonicacid metabolism leading to induction of Th2 biased strongimmune response and by controlling NK activity exerted anantiabortive effect on viruses. A subtype of estrogen receptor (ER) expressed in neutrophils from premenopausal women and in neutrophilsfrom men under different estrogen conditions was identified in a study.

The analysis was done on the association between the modifications in the expression of ER subtypes andneuronal nitric oxide synthase (nNOS) expression induced byestrogen. Neutrophils were isolated from premenopausal women during different stages of the menstrual cycle and from ten men for in vitro estrogen incubations. Outcomes showed that the neutrophils from premenopausal women expressed both ER-alpha and ER-beta subtypes which were increased in the ovulatory phase of the menstrual cycle. Neutrophilsderived from men also expressed ER-α and ER-β butonly ER-α expression

was enhanced by in vitro incubation with 17β-estradiol (10−8 mol/L). In vitro incubation of neutrophils from women with 17β-estradiol enhanced expression of both ER-α and ER-β subtypes.

Impact of Sex Hormones and Immunocytes Interaction:

Peripheral blood constitutes about 65% of the leukocytes: 32%granulocytes, 5–10% monocytes, and 30% lymphocytes. Infemales an increase in white blood cells counts was observed in the luteal phase of ovarian cycle and during pregnancy. Number of studies showed that decrease in the number of monocytesin follicular phase of cyclic females when estrogen levelis high as compared to an increase in males and postmenopausal females.

Estrogen in Immune System and Their Role in Immune System:

It is apparent that females have better immune capabilities with higher immunoglobulin levels and stronger humoral and cell-mediated immune responses than males. Studies showed their superior responses to a variety of antigens, their ability to reject allografts more rapidly, better in vitroresponse to mitogens and other in vitro immunologic assays, and relative resistance to the induction of immune tolerance. Females tend to have a reduced incidence of certain tumors and generally resist a variety of bacterial and viral infections and parasitic infestations more successfully than males. Cytotoxicity to certain viruses is much greater in females than males also the survival rate of females is greater than males because of their better immune capability.

A large amount of information supports the fact that hormones of the endocrine system are involved in the immune logical dimorphism in males and females. Major hormones included are growth hormone (GH), gonadal steroids, adrenal glucocorticoids, and prolactins. Complex hormonal interactions help in both developing lymphocytes and regulate mature immune cells. Effect of elevated estrogen levels to growth hormone secretion along with an increase in prolactins and thymosin release on the development of lymphocytes and stimulate immune cell functions in females was identified. Interactions of hormonal regulatory axes involving the hypothalamus, pituitary, gonads, adrenals, and thymus were also thought to be involved. Factors like IL-1 and IL-2 are elaborated by activated immune cells.

Conclusion:

Estrogen has long been known to play a role in the development of immune cell populations, going from immature to mature phenotypes. However, more recent studies demonstrate clearly that the outcome of immune responses are highly dependent upon the concentration of estrogen, the duration of the stimulation, and other factors present in combination with the hormone. Estrogen signaling manipulates T cell including the modulating T cells that would otherwise be beneficial in fighting viruses and cancer but become exhausted or lose polyfunctionality. A better understanding of all the ways estrogen regulates T-cell function is on the horizon and may be a key determinant to enhancing immune-based therapies for disease. So according to my suggestion we can isolate the immune components from the oestrogen and applying of immune components in male to preserve their health.

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