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Interactions Between the Gonadal Steroids and the Immune System

Charles J. Grossman

Summary. The immune system is regulated by the gonadal steroids estrogen, androgen, and progesterone, but the circulating levels of these steroids can also be affected by immune system function. Such interactions appear to be mediated through the hypothalamic-pituitary-gonadal-thymic axis and depend on pituitary luteinizing hormone released by thymic factors under the control of the gonadal steroids.

Historically the fields of reproduction and immunology have been classified as separate biological disciplines. A connection between these fields was first reported in 1898 when Calzolari (*1*) observed that the thymus of rabbits castrated before sexual maturity was larger than that of the controls. At the time this report first appeared it was not considered of much importance. However, 70 years after Calzolari's publication, researchers have begun to place greater emphasis on the interactions between the reproductive and immune systems. These reproductive-immunological interactions appear to be hormonally regulated, and the hormones involved originate from the thymus, the hypothalamus-pituitary unit, and the gonads. In this article, the role of the gonadal steroids in regulation of the acquired immune system is emphasized.

In humans, the innate and acquired immune systems constitute the total immune system. The innate system (also known as the nonspecific system) encompasses all reactions that are not antigen dependent, such as phagocytosis and inflammation. The acquired system (also known as the specific system) involves the antigen-dependent reaction of classes of lymphocytes called T cells and B cells. T cells are regulators of the cell-mediated immune response, B-cell function, and phagocytosis, whereas B cells are involved in humoral immunity and produce immunoglobulins called antibodies (*2, 3*).

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.

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Sex Steroids and Humoral Immunity

Many studies have demonstrated that immunoglobin production is greater in females than in males. In mice, females show a greater and more sustained response than males to the antigens bovine serum albumin (*4*) and hemagglutinin (*5*), and females also generate higher titers of the immunoglobins IgG (*6*), IgG1 (*7*), IgM (*6*), and IgA (*8*) than do male controls. Female hamsters also generate larger amounts of immunoglobin as measured both in vitro (*9*) and in vivo (*9, 10*) than do males, and this lessening of antibody production in the male coincides with the increase in sex steroid hormones at sexual maturity (*10*).

The mechanism responsible for the greater concentrations of antibody in females than in males is not completely understood at present. However, estrogens enhance the antibody response in mice (*11*) and appear to regulate the synthesis of uterine IgA and IgG in rats (*12*). This suggests that the spontaneous increase of immunoglobin levels during the estrous cycle may result from the action of estradiol in the uterus (*12*).

One possible mechanism for the stimulation of antibody production by estrogen is found in a report by Paavonen *et al.* (*13*) suggesting that estradiol can inhibit suppressor T-cell activity. Since suppressor T cells prevent B cells from manufacturing antibody, it follows that inhibition of suppressor T-cell function will enhance B-cell maturation and in-

crease antibody production (*13, 14*). Since B-cell maturation occurs within the lymphatic tissues, it is not surprising that in adult animals there is an increased proliferative response to antigen in spleen and lymph nodes as a result of estrogen treatment (*15*). On the other hand, treatment of neonatal female mice with the estrogenic compound diethylstilbestrol inhibits the development of immunocompetent T lymphocytes of the helper subclass but has no effect on the production of suppressor T cells. The function of helper T cells is to assist B cells in antibody production. Thus, in the absence of helper T cells and the presence of suppressor T cells, B-cell production of antibody is depressed (*16*).

Estrogen is not the only steroid hormone to affect antibody production. Treatment with the androgenic male steroid, testosterone alters immunoglobin synthesis in male rabbits (*17*) and in adult chickens (*18*). Therefore, the sexual dimorphism in the immune response appears to be based partly on differences in the major classes of circulating sex steroids.

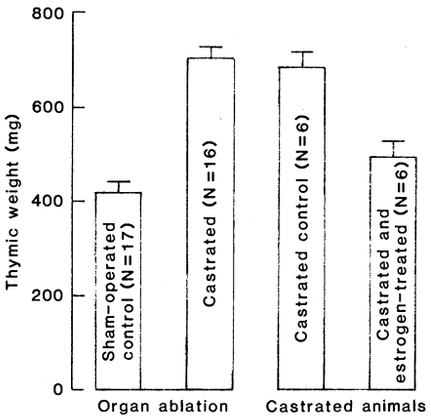

Fig. 1. Alterations in thymic weight with castration and estrogen treatment. Castrated male rats, 6 weeks of age, were treated for 3 days with estradiol at 15 μg/day (*34*).

Sex Steroids and Cellular Immunity

Not only humoral immune responses but also the cell-mediated immune response can be affected by sex steroid hormones. One example of sex steroid regulation of the cellular immune response is the depression of suppressor T-cell activity by estradiol (*13, 14*). Another example is the increase in the time required for the tissue rejection response in guinea pigs (*19*), rabbits (*20*), rats (*21*), mice (*22*), and humans (*23*). Depression of the cell-mediated immune response by estrogen leads to increased mortality in both male and female guinea pigs and male and female mice infected with the parasitic protozoan *Toxoplasma gondii*; castration increases resistance to this infection (*24*). Castration also shortens skin graft rejection time in both male and female mice (*25*), suggesting that removal of the gonads activates the cell-mediated immune response. Since castration leads to a decrease in circulating sex steroid hormones, these studies suggest that sex steroid hormones such as estrogen depress T-cell function and that removal of such hormones by castration enhances T-cell function and thus stimulates the cell-mediated immune response.

Certain autoimmune disorders are significantly influenced by sex steroid hormones. For example, in the mouse (*26*) and human (*27*), lupus erythematosus is more prevalent in females than in males. Accordingly it has been shown that androgens depress and estrogens accelerate the disease process. Androgen treatment appears to benefit patients suffering from idiopathic thrombocytopenic purpura (ITP), which is more commonly found in females. Menstruation, however, exacerbates ITP (*28*), probably as a result of the decreasing levels of circulating sex steroids. Finally, in humans, rheumatoid arthritis is more prevalent in females than in males, and joint inflammation is reduced significantly in many using oral contraceptives (*29*).

A culture system was used to clarify the underlying mechanisms by which castration or sex hormone treatment can alter cellular immunity. Lymphocytes extracted from rat thymic tissue were incubated for 3 days in culture medium containing 20 percent rat serum. In such cultures, both T-lymphocyte mitosis and DNA synthesis are stimulated by the addition of a mitogenic substance such as phytohemagglutinin or concanavalin A, and increases in DNA content are then monitored by cellular incorporation of [^{3}H]thymidine. Addition of estradiol, testosterone, or dihydrotestosterone to these cultures at physiological concentrations along with normal rat serum has no effect on T-cell DNA synthesis regardless of the mitogen used (the result in disintegrations per minute in the control assays is not significantly different from that in the assays in which sex steroid hormones were added to the culture medium (*30, 31*). However, when serum prepared from castrated male rats was added to T-lymphocyte cultures along with these mitogens, a marked stimulatory effect was observed (with concanavalin A, the values were 1269 dpm for controls and 5646 dpm for castrated animals; with phytohemagglutinin, the values were 823 dpm for controls and 1814 dpm for castrated animals) (Table 1). Serum prepared from castrated rats treated in vivo with physiological concentrations of estradiol had a marked inhibitory effect on T-cell function (with conconavalin A, the values were 5646 dpm for castrated animals and 790 dpm

Table 1. Results of blastogenic transformation of normal thymocytes incubated in the presence of rat serum. Serum was prepared from various groups of male rats, allowed to clot, centrifuged at 800*g* for 15 minutes, decanted, and stored at −30°C. Before being used, the serum was sterilized by filtration and inactivated with heat. Blastogenic assays were carried out in microtiter plates with 0.2 ml of cell suspension, rat serum samples, and the mitogens concanavalin A or phytohemagglutinin. After 3 days of incubation at 30°C, the cultures were pulse-labeled with [^{3}H]thymidine and collected on glass filters for counting of ^{3}H activity. The mitogen concanavalin A is thought to preferentially stimulate suppressor thymic lymphocytes, whereas phytohemagglutinin appears to affect a more diverse population of thymic lymphocytes, including both helper and suppressor cells (*30, 31*). Statistical significance between groups was measured with the Welch test for two samples with unequal variance. Values are means ± standard error of the mean. *N* is the number of separate animal preparations used to generate thymocytes for the assay (*30, 31*). Numbers in parentheses indicate significant differences from values for castration only.

Treatment	*N*	Blastogenic activity (dpm)		
		Without mitogen	Mitogen added	
			Concanavalin A	Phytohemagglutinin
Normal controls	77	383 ± 40	1269 ± 184	823 ± 73
Castration only	56	439 ± 49	5646 ± 769	1814 ± 159
Castration + estradiol	6		790 ± 115 ($P < 0.001$)	802 ± 230 ($P < 0.001$)
Thymectomy only	26		1081 ± 143 ($P < 0.001$)	1239 ± 157 ($P < 0.001$)
Castration + thymectomy	18		2014 ± 397 ($P < 0.001$)	743 ± 7 ($P < 0.001$)

for castrated animals given estradiol; with phytohemagglutinin, the values were 1814 dpm for castrated animals and 802 dpm for castrated animals given estradiol) (Table 1). Finally, serum prepared from castrated thymectomized animals lost its ability to stimulate T lymphocytes (with concanavalin A, the values were 5646 dpm for castrated animals and 2014 dpm for castrated thymectomized animals; with phytohemagglutinin, the values were 1814 dpm for castrated animals and 743 dpm for castrated thymectomized animals) (Table 1). Such results suggest that in the presence of estradiol the release of thymic serum factor is inhibited, whereas in the absence of estradiol (as by castration) this thymic factor is stimulated (*30, 31*).

After castration, there is an increase in the mass of peripheral lymph nodes, spleen (*32*), and thymus (*32, 33*) (Fig. 1). Castration before puberty delays the onset of thymic involution (which normally takes place at puberty) and instead produces thymic hypertrophy (*32, 33*) (Fig. 1), whereas castration after puberty reverses thymic involution and also results in thymic hypertrophy (*32, 33*).

Along with the increase in thymic mass induced by castration, there are structural alterations in the thymus of castrated animals. The size of the cortex and medulla are increased in the thymic tissue prepared from castrated male and female mice, and cellular density is greater (*32*). Since castration leads to an increase in the number of glucocorticoid-sensitive cells while the number of cortisone-resistant cells remains unchanged, there may be a greater production of thymic lymphocytes originating from precursor cells after castration (*16*). Estrogen-treated rats have gross alterations of thymic tissue architecture, and histological studies show atrophy of the lobules, increased fat content of the gland, and destruction of thymic lymphocytes (*33*).

Because these thymic structural alterations depend on the amount of circulating sex hormones, it follows that in the thymus, as in other hormonally responsive tissues, sex hormone receptors mediate these responses. Such steroid receptors have been identified and characterized in thymic tissue for estrogen (*34–36*), androgen (*37, 38*), and progesterone (*39*). According to a number of studies, these receptors are present in the reticuloepithelial matrix of the thymus but not in thymic lymphocytes (T cells) (*34, 35, 37, 39*) (Table 2). However, in two studies, estrogen and androgen receptors were found in T cells (*40, 41*). Differences in the experimental conditions under which the receptors were measured (assay sensitivity, tissue preparation, or presence of sodium molybdate in the buffers) may explain the differences in these observations (*42*).

The presence of such receptors in thymic tissue supports the concept that sex hormones can regulate immune function. This is an especially appealing idea when one considers that the thymus produces peptide hormones that mediate lymphocyte actions (*43*). Thus, it is possible that the sex hormones may play a role in regulating the biosynthesis and secretion of such thymic hormones, which in turn may affect immune responsiveness.

Immune Response During Pregnancy

Increases in circulating levels of sex steroid hormones during pregnancy can clearly modify immune responsiveness. Hormonal increases take place in all mammalian species during pregnancy and may potentially assist in preventing the maternal-fetal rejection response. If this rejection response is not depressed, termination of pregnancy may take place before completion of term (*44*). However, in most pregnant women, the cell-mediated immune response is markedly depressed (*45*) and pregnancy is maintained. This can also account for the observation that human skin homografts survive longer on pregnant hosts than on nonpregnant hosts (*46*).

Similar findings have been reported for rat skin homografts implanted within the uteri of pregnant and nonpregnant rats. In this system the depression of the cell-mediated response and tissue rejection is dependent on increases in progesterone-estrone combinations (*47*). Furthermore, increased amounts of estrogen-progesterone combinations appear to prolong skin graft survival in mice (*48*) and monkeys (*49*), while progesterone facilitates xenogenic cell implantation in the hamster uterus (*50*). Progesterone treatment also prolongs the survival of allografts of skin in rabbits and rats (*51*). Finally, progesterone at concentrations found in the human placenta (2×10^3 to 6×10^3 ng per gram of tissue) acts as an immunosuppressive agent on lymphocyte cultures stimulated by allogenic antigen (*52*). These results indicate that progesterone participates in the regulation of the immune response during pregnancy.

In pregnant mice, thymic involution and atrophy are observed along with a reduction in the number of cortical thymocytes, while the number of medullary (steroid-resistant) thymocytes remains unchanged (*53*). These medullary thymocytes show a greatly reduced mitogenic response (*53*), and it is possible that the cortisone-resistant cells unaffected by castration (*6*) are the same as the steroid-resistant cells of the thymic medulla observed in pregnancy (*54*). Furthermore, the cortical thymocytes that are reduced in number during pregnancy (*54*) may be the same as the glucocorticoid-sensitive cells that increase in number after castration (*6*).

The Hypothalamic-Pituitary Gonadal Thymic Axis

Studies of mice thymectomized shortly after birth indicate that the thymus plays a role in immune regulation of sex hormone levels. Removal of the thymus 3 days after birth results in ovarian dysgenesis, a condition characterized by lymphocyte infiltration of the follicles, a decline in oocyte numbers, and interstitial cell hypertrophy (*55*). Thymectomized animals also show a reduction in serum progesterone, serum estrogen, lu-

Table 2. Steroid receptor characteristics of normal rat thymus. Thymic tissue obtained from 6-week-old male rats was separated into reticuloepithelial matrix and thymic lymphocyte fractions by means of a stainless steel screen. Both fractions were homogenized in tris-EDTA buffer and centrifuged at 120,000*g* for 30 minutes to produce the supernantant fractions termed cytosols. The presence of steroid binding receptor protein in these two cytosolic fractions was measured by Scatchard type kinetic assays (*59*). Values are means ± S.E.M. for *N* separate animal preparations.

Fraction	*N*	K_a ($\times 10^9 M^{-1}$)	Steroid-binding receptor protein	
			Picomoles per milligram of tissue	Femtomoles per milligram of protein
		Dihydrotestosterone receptor		
Reticuloepithelial matrix	11	2.44 ± 0.35	0.19 ± 0.01	4.87 ± 0.22
Thymocytes	11	0	0	0
		Estradiol receptor		
Reticuloepithelial matrix	10	6.05 ± 0.73	0.315 ± 0.03	6.69 ± 0.58
Thymocytes	10	0	0	0

teinizing hormone (LH), follicle-stimulating hormone (FSH), and growth hormone (GH). A reduction in gonadotropin secretion has also been reported in the congenitally athymic mouse (*56*).

Two separate but interrelated mechanisms for the interaction between the thymus and gonads have been suggested. The first of these depends on the level of maturity of the functional T-lymphocyte classes. In animals thymectomized at birth, helper T cells are present but suppressor T cells are absent. The lack of functional suppressor T cells is explained by the inability of these cell types to mature in the absence of the thymic microenvironment. In the absence of suppressor T cells and the presence of helper T cells, B cells produce autoantibody to oocytes (*55*).

The second mechanism for thymic gonadal regulation is dependent on the hormonal interactions between the hypothalamus, pituitary, gonads, and thymus (the HPG-thymic axis). Experiments performed in vitro with a hypothalamic-pituitary perfusion system showed that two thymic hormones, thymosin fraction 5 and thymosin β_4 stimulate the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Gonadotropin-releasing hormone in turn stimulates LH release from the pituitary (*57*). Since thymectomy removes the source of thymic hormones and ultimately decreases LH release from the pituitary (*55*), it is not surprising that early thymectomy also reduces FSH, GH, progesterone, and estradiol and, as a result of the lower sex steroid levels, also delays the onset of puberty and vaginal opening (*55*). Treatment of mice with estradiol in vivo also reduces the circulating levels of thymosin α_1 (*58*), possibly through direct estrogen receptor interaction at the level of the thymic reticuloepithelial cell. Furthermore, injection of animals with thymosin fraction 5 causes a decrease in ovarian weight as well as marked thymic involution (*58*). The effects of thymosin fraction 5 on ovarian weight and thymic involution are probably mediated through gonadotropin release and subsequent alterations in circulating levels of sex hormones.

A tentative scheme for the hormonal interactions of the HPG-thymic axis is presented in Fig. 2. Gonadotropin-releasing hormone from the hypothalamus stimulates LH release from the pituitary, and LH stimulates sex steroid (estrogen or testosterone) production by the gonads. Through a negative feedback mechanism, this causes GnRH release from the hypothalamus to be depressed

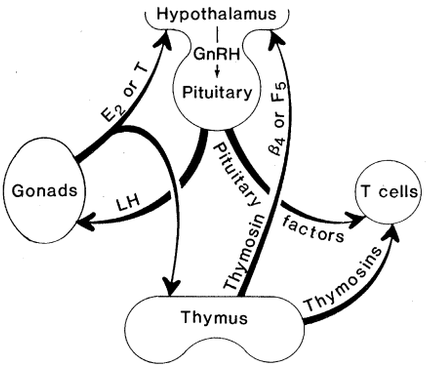

Fig. 2. Hypothetical scheme for the regulation of thymocytes (T cells) by the HPG-thymic axis (*59*).

and LH release from the pituitary to be inhibited. Increasing levels of sex steroids from the gonads depress thymosin release from the thymus, whereas decreasing levels of sex steroid may facilitate thymosin release (*30, 31*). Increasing levels of thymosin stimulate GnRH release from the hypothalamus. Finally various different thymosins modulate T-cell function by stimulating maturation of either helper or suppressor T cells (*43*). Other pituitary factors (for example GH) (*59*) may regulate T-cell function directly.

Although estrogens and androgens have been reported to be both immunoinhibitory and immunostimulatory, estrogens and androgens act mainly to suppress the cell-mediated immune system. However, estrogens and androgens may not necessarily suppress the same lymphocyte populations of the cell-mediated immune system. Estrogens can also act as stimulators of the humoral immune system, and this effect may be regulated through the cell-mediated immune system by stimulation of helper and inhibition of suppressor lymphocytes. Androgens may also stimulate the humoral immune response, possibly because they can be metabolically converted to estrogens. The ratio of estrogen to androgen may determine whether the circulating hormones will be immunostimulatory or immunoinhibitory. Furthermore, the concentration and availability of estrogen and androgen receptors in target cells of the immune system must act as a regulatory influence on hormonally mediated immune responses. Finally, the HPG-thymic axis appears to play a significant role in the mechanism by which the sex hormones regulate the immune response and implies that important interactions exist between the nervous system, the endocrine system, and the immune system.

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The World Bank's Support for Science and Technology

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Summary. The World Bank, the largest aid-granting agency in the world, has played a substantial but largely unsung role in helping the scientific and technological development of developing countries. Its investments, totaling $15.5 billion in fiscal year 1984, involve choosing appropriate technology and financing local technological development. Since 1980, the Bank has lent $0.5 billion for agricultural research and about $1 billion for scientific and technological education. It contributes to and mobilizes finances for large international research programs in agriculture and the health sciences. It supports research on labor-based construction, low-cost sanitation, renewable energy resources, and control of traffic congestion. It provides training in the technological aspects of development policy. As funds for aid become scarce, the Bank is reexamining its approach to science and technology.

The World Bank is the largest multilateral organization for development assistance in the world. Its loans to developing countries in fiscal year 1984 totaled $15.5 billion (*1*). These loans support about 230 development projects in agriculture, rural development, energy, education, industry, telecommunications, transportation, water supply, sanitation, urban shelter, population, health, and nutrition.

The selection of appropriate technology and the building of the local technological capacity are integral and essential aspects of the Bank's projects although not their primary objectives. The technology includes not only equipment (hardware) but also governmental policies and institutional and administrative arrangements necessary to implement the project (software). A project intended to increase the production of food-crops, for example, would be based on a broad analysis of the agricultural sector, and it may include the institution of governmental policies designed to increase the prices paid to farmers or to improve marketing and distribution.

The Bank has financed many agricultural research and extension projects that stress the creation and distribution of technology with direct, practical value to low-income farmers. It was among the first institutions to finance venture-capital companies and programs to support innovation in industrial enterprises in developing countries. By so doing, the Bank has promoted government policies and programs that create a demand for improved technology and local decision-making capacity while avoiding the traditional emphasis on government-owned institutes. It has identified or developed improved, low-cost technology for civil works construction, sanitation, and other critical activities. Most recently, the Bank has assisted in training policy-makers and research managers in the technological aspects of development policy, and it has also begun to assist developing countries in building scientific and technological infrastructures.

The Bank is only one of many agencies that contribute to scientific and technological development in developing countries. Still, this aspect of its work may be less familiar than similar work done by specialized agencies of the United Nations, such as the Food and Agricultural Organization (FAO), the World Health Organization (WHO), and the U.N. Educational, Scientific, and Cultural Organization (Unesco), and by bilateral aid agencies such as the U.S. Agency for International Development.

To scientists and engineers who are accustomed to grant financing, the willingness of developing countries to use large sums of borrowed money to support science and technology may be a surprise, especially since these projects have a relatively long pay-off period. This shows that they consider investment in science and technology to be worthwhile, even with borrowed money. It also indicates that, in the long run, governments expect investments in science and technology to pay their own way, at least in a broad sense.

Mechanisms of Bank Support for Science and Technology

The Bank supports science and technology by four mechanisms.

1) As a service, within the framework of a loan for a development project, the Bank provides technical assistance in the choice, implementation, and operation of technology and in the development of local technological capacity.

2) The Bank lends money, through the projects it supports, for training, research, innovation, development of scientific and technological capacity, and

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