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Review

Hormonal modulation of the immune system — A spotlight on the role of progestogens

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ABSTRACT

This article reviews the effects of progestogens on the innate and adaptive immunity and its role in the pathogenesis of autoimmune diseases including systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis.

The interplay between the sex hormones such as progestogens and the immune system is very complex. Multiple factors affect immunomodulatory effects of the progestogens including fluctuations in the endogenous sex hormone levels, stress, use of exogenous hormones (dose, route and the timing of administration), and alterations in the hormonal metabolism. Although immunomodulatory effects of progesterone, especially progesterone's effect on T cells, T cell subsets and their ratios, dose effects, and the use of synthetic progestins have been studied, there are still wide open areas for further explorations of the progestogens' multifaceted impact on the immune system. Better understanding of the intricate immunomodulatory effects of the progestins may pave the path to developing clinically meaningful therapeutic interventions in certain autoimmune diseases.

Contents

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1. Introduction

Autoimmune diseases encompass a wide spectrum of between 70 and over 100 different disorders affecting 5–10% of the world population [1,2]. The disease induction and perpetuation of autoimmunity are multifactorial and complex. In general, autoimmune diseases are thought to result from an intricate interplay of genetic, epigenetic, gender, race, hormonal, environmental, and stochastic factors [2,3]. The complexity of autoimmune mechanisms has been likened to a mosaic, where rearranging much of the same starting materials, such as pieces of genetic, hormonal, immunologic, and environmental factors in different orders, yield different pattern or a variation, of the same disease [4].

2. Gender and autoimmunity

Gender plays a critical role in the incidence and prevalence of autoimmune diseases. Females have a higher prevalence of autoimmune diseases [2]. In the prototypic autoimmune disorder, systemic lupus erythematosus (SLE), the female-to-male ratio is 10–12:1 [5]. This striking predilection for female occurs in both mice and man [2,6]. SLE is not unique in this regard. In a variety of other autoimmune diseases such as Sjogren's syndrome, autoimmune thyroid disease (AITD) including Graves' disease (GD) and Hashimoto's thyroiditis (HT), and scleroderma more than 80% of the affected are women [2]. Likewise, in rheumatoid arthritis (RA), multiple sclerosis (MS), and myasthenia gravis, the affected are 60–75% women [2]. The notion of X-chromosome dose effect has been unraveled with recent genetic studies. Using a single nucleotide polymorphism (SNP) genotype screen for X-chromosome abnormalities which are subsequently validated by karyotyping, Klinefelter syndrome (47, XXY) was found to be 10-fold more prevalent in males with SLE than in general population [7]. Indeed, having an extra X-chromosome like females, increases the risk of SLE in Klinefelter syndrome. Several lines of evidence from observational, experimental, and epidemiological studies indicate that being female per se or having an extra X-chromosome, confers a greater risk of developing both multiorgan and organ-specific autoimmune diseases [2,4,8].

2.1. Sexual dimorphism in immunity

There is clear disparity between the immune responses of female and male. This well-established concept of sexual dimorphism is seen in both human and animal models [9]. Females generally have a more vigorous humoral and cellular immunity than males [9]. Females experience lower burden of microbial infections by mounting stronger and longer lasting humoral and cellular immune responses [9,10]. This is manifested by higher absolute numbers of circulating CD4 T cells, higher levels of circulating antibodies, enhanced cytokine productions in response to infections, and more rapid rejection of skin allografts compared to males [9,11]. The heightened immune response that makes females more resistant to infections, however, also rendered them more susceptible to autoimmune diseases [12].

2.2. Immunomodulatory effects of sex hormones

Sexual dimorphic modulation of immune response is best seen in terms of infections, in the context of menstrual cycle, and during pregnancy [9–13]. Male gender is associated with a less reactive immune system and hence an independent risk factor for major infections after surgery [13]. These observations provide evidence that female sex hormones, estrogen and progesterone, have differential effects on the pathogenesis of different autoimmune diseases. In RA and SLE, the severity of the disease symptoms varies with the phases of the menstrual cycle [14,15]. Another evidence for the influence of sex hormones on autoimmune diseases comes from changes in disease severity of RA, MS, and SLE during pregnancy [2,16,17]. In both RA and MS, the disease activity decreases throughout pregnancy, and remits in most individuals during the third trimester when both estrogen and progesterone concentrations are highest [16,17]. This is followed by an inevitable flare of disease activity in the post-partum period when both estrogen and progesterone concentrations normalize [16,17]. In contrast, the disease activity of SLE either gets worse or remains unchanged during pregnancy [2]. The female immune system is characterized by not only higher reactivity which translates to better protection from infections, but also increased autoreactivity. The incidence of the prototypic autoimmune disease, SLE, is highest between menarche and menopause when the female sex hormones are at their peak.

2.3. Sex hormones and autoimmunity

The female predominance in various autoimmune diseases, the sexual dimorphism of immune response, and the immunomodulatory effects of sex hormones generated tremendous interest in investigating the influence of sex hormones in autoimmunity. Scores of research was launched focusing on the effects of estrogen, progesterone, testosterone, and prolactin on autoimmune diseases [2,4,6,18–20]. While considerable studies have focused on estrogen, testosterone, and prolactin, much less is known about progesterone. This review will summarize our current understanding of the role of progestogens in autoimmune diseases.

2.4. Progesterone and immune modulation

2.4.1. Progestogens

Progestogens encompass both natural occurring progesterone and synthetic progestins. Progesterone, a natural sex steroid hormone derived from cholesterol, is produced by the adrenal glands, ovaries (by the corpus luteum), testes, brain, and in the placenta during pregnancy, and it is an intermediate in the biosynthesis of androgens, estrogens, and corticosteroids [21]. The pleiotropic functions of progesterone include physiologic role in the luteal phase of the menstrual cycle; key hormone in maintaining pregnancy; and profound effects on regulation of immune responses [22]. Progesterone is found in both female and male of both humans and rodents. The basal levels of progesterone between male, non-pregnant female rodents, and humans do not vary much [23]. During pregnancy in both mice and humans however, progesterone could rise up to 10-fold basal rate in the maternal circulation and up to 100-fold maternal circulation in the human placenta [24]. Structurally, progesterone consists of four interconnected cyclic hydrocarbons, and like other steroids it is hydrophobic. Progesterone contains ketone and oxygenated functional groups, as well as two methyl branches.

Progestins are man-made agents commonly used for contraception and hormone replacement therapy. Progestins differ widely in their chemical structures, functions, metabolism, pharmacokinetics, and potency [25]. When classified according to their chemical structure, progestins may be described as resembling progesterone or testosterone [25].

Progestins structurally related to progesterone are divided depending on the presence (pregnanes) or absence (norpregnanes) of a methyl group at carbon 10; then further divided depending on presence or absence of acetate-containing group [25]. The pregnane compounds with an acetate group include: medroxyprogesterone acetate (MPA), megestrol acetate, chlormadinone acetate, and cyproterone acetate. The pregnane compounds without an acetate group include: dydrogesterone and medrogestone. In the 19-norpregnanes containing an acetate group, there is nomegestrol acetate and nesterone. In the 19-norpregnanes without an acetate group, there is demegestone, promegestone, and trimegestone. Progestins related to testosterone can be subdivided into those with and without a 17-ethinyl group. Seventeen ethinylated progestins consist of the families of norethindrone (estranes) and levonorgestrel (13-ethylgonanes). They include norethindrone, norethindrone acetate, ethynodiol diacetate, norethynodrel, lynestrenol, and tibolone. In the 13-ethylgonane category, there is levonorgestrel, desogestrel, norgestimate, and gestodene. Finally, the

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