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Review

COVID-19 and the role of estrogen in the immune response

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Abstract: We conducted a study using the keyword search (estrogens and COVID-19) in various databases through June 2022. All articles were published in English. In the context of the COVID-19 pandemic, gender differences were found in the course and outcomes of the disease. The goal of this review was to summarize the knowledge of the mechanisms underlying gender-based differences in COVID-19, with a focus on the role of estrogens. The article discusses the involvement of estrogen in the implementation of the immune response to viral infection. Separate sections of the review are dedicated to the effect of estrogens on innate and adaptive varieties of immunity. We concluded that there is great potential for future research on deciphering the effect of hormones on human physiology and immune responses to explain the heterogeneity of human pathogenic responses.

Keywords: COVID-19, estrogens, immunity.

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Introduction

The COVID-19 pandemic has caused global concern in the professional community and has had a significant impact around the world. Striking gender-based differences were discovered: men were more likely to have severe infections and exhibit higher mortality, with similar rates of infection for both sexes [1, 2]. This pattern was also observed during other coronavirus epidemics [3, 4]. The discrepancies between the course and outcomes of the disease were most likely multifactorial phenomena: they could be associated with gender-based social, behavioral and biological differences. Biological factors include the production of sex hormones. Differences in their concentrations help explaining the immune response and severity of COVID-19 in men [5]. In a study of patients with COVID-19 during hospitalization, sex hormone levels were associated with higher concentrations of inflammatory cytokines, disease severity, artificial ventilation use, and mortality. Gender-based difference persisted regardless of other risk factors for severe outcomes, including age, body mass index, comorbidities, smoking, and race [6]. In this review, we will attempt to explain some of the underlying mechanisms of gender-based differences, with a focus on the role of estrogen.

Estrogens and their signaling mechanisms

Estrogens (Es) are a class of sex hormones, the role of which is in regulating the development and functioning of the female reproductive system well understood. However, their activity can modulate multiple pathways in the body, including immune responses and proinflammatory signals. [7]. There are four forms of endogenous Es, of which the estradiol (E2) has the highest estrogenic activity and concentration in the bloodstream. Multiple enzymes control E synthesis on the basis of cholesterol [8]. In women, Es are synthesized mainly in the ovaries, as well as in the placenta during pregnancy; after menopause, the level of Es produced by the ovaries decreases sharply, and most of them are formed in secondary tissues [7]. The effects of Es are primarily implemented via their binding to estrogen receptors (ERs) through two different mechanisms. The *classical mechanism* involves the binding of an E to the ER in the nucleus to activate or repress specific genes. To stimulate quick responses, Es can act through *non-genomic mechanisms*. The functions of Es are determined by the location and type of the receptor. Currently, several receptors are known, three of which are the most extensively studied: estrogen receptor alpha (ERα), estrogen receptor beta (ERβ) and G protein-coupled receptor (GPER1/GPR30) [9]. Further adaptation of estrogenic effects is achieved through different splice variants and patterns of their expression in tissues, which creates the possibility of various estrogen-induced responses throughout the body [10].

Estrogens and immunity

Gender-based differences in immune responses are well-known. As a rule, in the fight against viral infections, the immune system in women works differently than in men, generating a stronger immune response, leading to the elimination of the virus. In general, the level and duration of antibody production in women is higher than in men [3].

Sexual dimorphism is also seen in the coronavirus-associated inflammatory response, which occurs as a result of dysregulation of the immune system response. Indeed, elevated levels of interleukin (IL)-6, C-reactive protein, and cytokines segregate with

acute respiratory distress syndrome more frequently in men than in women. The fact that a stronger immune response to viral infections in women is associated with a more modest inflammatory response to COVID-19 is paradoxical. The explanation for this surprising behavior is that the hyperinflammatory response observed in male patients with COVID-19 is a natural consequence of ineffective early antiviral immunity observed in men [3].

Publications from around the world present a large amount of data on the effect of E on immune responses, albeit the obtained results are contradictory. Various groups of scientists report pro- and anti-inflammatory effects, or even dual action depending on the specific type of studied cytokines/cells and the concentration of the hormone [7, 11]. In part, this may be due to pleiotropic ER expression and multiple genomic and non-genomic effects of Es in various cell types [12]. Higher levels of E inhibit the proinflammatory innate immune response, enhance the T helper 2 (Th2) and humoral immune responses, and have a protective effect on endothelial cell function. At low doses, Es promote proinflammatory responses, including increased production of proinflammatory cytokines and an enhanced cell-mediated immune response. A low level of Es induces the differentiation of monocytes into inflammatory dendritic cells, increases the production of IL-1,4,6, TNFα and interferon (IFN)α, as well as promotes T helper 1 (Th1) and cell-mediated immune responses [5, 13, 14, 15].

Our understanding of the exact mechanisms underlying these differences is still vague; however, published data support the existence of gender-based diversity in the composition, epigenetic regulation, and function of immune cell populations [3].

Innate immunity

The innate immune system launches an initial response to a viral infection. Innate immune cells with specialized functions include neutrophils, eosinophils, basophils, mast cells, monocytes, dendritic cells, and macrophages, main ability of which is to rapidly and broadly respond to pathogen penetration, most often causing an inflammation. ERs were detected on all cells of the innate immune response [16, 17], meaning that female sex hormones modulate their activity [18].

E2 has an anti-inflammatory effect on the innate immune response via reducing the release of inflammatory cytokines by monocytes and macrophages, inhibiting NK cell cytotoxicity, delaying neutrophil apoptosis, and enhancing the expression of neutrophil annexin-1 [13, 17, 19]. Es can regulate macrophage polarization [12]. Female sex hormones also influence the dendritic cell population, with E2 signaling through the ERα to increase the number of new dendritic cells during inflammation. In plasmacytoid dendritic cells, which are mainly involved in antiviral responses, E increases the release of cytokines important for an effective immune response. In addition, E2 suppresses the immune functions of endothelial cells, such as stimulating the adhesion of leukocytes and their migration to infected tissues [20].

Adaptive immunity

The adaptive immune response develops over time, retaining information about previous infections and activating a specific and long-term response. Adaptive cells are highly specialized: lymphocytes (T and B) carry unique receptors that recognize specific rather than general patterns.

T lymphocytes are one of the main cell types responsible for our long-term immunity. T cells can be categorized into two groups based on the presence of specific markers on the cell surface: CD8+, or *cytotoxic T cells*, and CD4+, or *T helper cells*. As their names suggest, these two populations of T cells perform different functions in the course of the immune response: CD8+ primarily target the death of infected or damaged cells, while CD4+ secrete pro- and anti-inflammatory effector molecules to coordinate larger immune responses. CD4+ are subdivided into Th1 and Th2 [21, 22]. Another part of the adaptive immune response encompasses B lymphocytes. Upon contact with an antigen or stimulation by T cells, they transform into plasma cells that produce antibodies. In addition, B cells can act as antigen-presenting cells and can produce cytokines.

Women have more B cells, higher baseline immunoglobulin content, and higher proliferation of regulatory T cells, cytotoxic T cells and CD4+ T cells. They are also characterized by a higher CD4+/CD8+ ratio [14, 21]. This contributes to the rapid response of the body to infectious agents.

ERs are expressed on adaptive immunity cells, allowing female sex hormones to affect downstream signaling pathways, thereby generating one or another immune response [16]. The published studies comparing the expression levels of specific ERs in various types of immune cells reported that B cells exhibited the highest level of ER expression with an increased ratio of ERβ to Erα, compared with CD4+ and CD8+ T cells [7]. It was established that ER signaling promotes the type 2 immune response required for virus elimination and repair of damaged tissues [23].

Besides, Es were reported as critical for the development, differentiation and the function modulation of various T cell phenotypes [7]. E2 signaling through ERα was revealed to interfere with Th1 and Th17 cell differentiation, providing a protective mechanism against inflammation. Also, physiological concentrations of E2 promote T lymphocyte proliferation and interferon gamma (IFN-γ) production *in vitro*. In Th2 cells, ERα stimulation with E2 increases IL-4 expression [18].

Es inhibit the production of Th1-mediated proinflammatory cytokines and stimulate the production of Th2-mediated anti-inflammatory cytokines [20]. Varying levels of the hormone during the menstrual cycle also influence the immune response, with a shift towards the Th2-type response observed during the luteal phase. Es promote the proliferation and development of B cells, enhance their activity and antibody production via increasing the expression of the membrane receptor CD22, protein phosphatase 1 containing the Src homology 2 domain (SHP-1), and the protein factor Bcl-2 [18]. The genes essential for this are regulated by Es. High E level just before ovulation correlates with B cell count and antibody levels [19]. Overall, the correlation between elevated levels of circulating antibodies and Es was confirmed by many researchers. It was established that women have a higher production of antibodies and a more effective response to the vaccine [7, 14, 15, 19, 21]. Similar pattern applies to the production of antibodies to coronavirus [5, 24]. A study conducted at the very beginning of the epidemic in Wuhan demonstrated that the concentration of immunoglobulin G to SARS-CoV-2 was significantly higher in women than in men, and it remained so during four weeks after their hospitalization [14].

Estrogens and the implementation of immune response

Toll-like receptors (TLRs) are expressed by immune cells. TLRs are considered key pathogen recognition receptors [25]. They are localized both on cells of innate immune system (*dendritic cells, macrophages, natural killer cells*) and on cells of adaptive immune system. There are ten different types of TLRs in the human genome, which are coded as TLR1-10 [26]. TLR expression is gender dependent. TLR-3, TLR-7, and TLR-9, which recognize viral nucleic acids, target women, while TLR-2 and TLR-4, which recognize bacterial nucleic acids, target men. Among them, TLR-7 should be specifically noted: avoiding inactivation, it is transcribed on both X chromosomes, which leads to its greater expression in the immune cells of women [15]. Recognizing a viral infection, TLR7 triggers the production of type I IFN with antiviral functions aimed to control viral replication and activate the adaptive immune response [25]. Since TLR7 is activated by E, this improves the prognosis of COVID-19 in women.

E regulates the type I IFN response through several potential mechanisms. One of the most common mechanisms is the complete prevention of type I IFN production. It was shown that this may occur through direct interactions between ERα, GPER1, and NF-κB. These interactions can be implemented either via ERβ occupying NF-κB transcription sites or through ERs inducing expression of the NF-κB inhibitor Iκβα. Also, Es can activate GPER1 to directly suppress IFN signaling. Therefore, Es can affect two early stages of the antiviral immune response: the production of IFNs and the response to them [7].

In addition to interferons, cytokines play an important role in the implementation of the immune response. Their production is also the result of NF-κB activation. An increase in E levels leads to the suppression of many proinflammatory cytokines by blocking signaling through NF-κB [7]. Thus, Es have the ability to reduce the cytokine storm that develops at the onset of SARS-CoV-2 infection, which triggers damage to cells and tissues [17].

In SARS-CoV-2 infection, the innate immune response is the main driver of virus eradication and disease pathogenesis. In particular, E contributes to an increase in the number of neutrophils in response to a viral infection [13, 19]. Type I IFNs, including IFNα, limit viral infection, initiate tissue repair, and program the adaptive immune system to accelerate virus clearance. A sustained, limited, and timely IFN-I response is protective, but the abnormal production of cytokines and chemokines (many of which are interferon-stimulated genes) contributes to dysfunction during SARS-CoV-2 infection, including the development of acute respiratory distress syndrome [13].

It was shown that in the early phase of the antiviral immune response to SARS-CoV-2 infection, proinflammatory mediators (IL-6, CCL2, and CXCL1) undergo similar increases of concentrations in both males and females, and 72 hours after infection, their levels in male mice are higher than in females. The explanation for this finding is the suppression of E activation of monocytes and macrophages, along with NF-kB in macrophages [18]. Such immune modifications determine the strength of the inflammatory response and affect the likelihood of progression of severe clinical outcomes in patients with COVID-19.

Estrogens and direct antiviral action

Currently, experimental data on the direct antiviral activity of Es are accumulating. S.M. Smith et al. infected monkeys with immunodeficiency virus after oophorectomy. It turned out that 100% of the monkeys that received additional E did not become infected, in contrast to those that did not receive the hormone [27]. M.F. Hannah et al., when conducting experiments on rats infected with Seoul hantavirus, revealed active transcription of many anti-inflammatory genes and genes associated with the innate immune system in females. They also discovered that these genes contained E response elements [28].

E affects many viruses at the molecular level, especially in the mechanism of virion replication and maturation. It was demonstrated *in vitro* that E2 disrupted the life cycle of the hepatitis C virus. The hormone blocked the assembly and release of the virus. The authors of the experiment proposed that not only the modulation of intracellular homeostatic processes of the host, but also the direct mechanism of E action on the virus, explained the observed phenomenon [29]. ERs were also shown to repress the transcriptional genes of viruses. One example is hepatitis B virus infection, in which ERα prevents viral gene expression by binding hepatocyte nuclear factor 4α to enhancer I of this virus [30]. In addition, inhibition of human immunodeficiency virus E2 replication was found through activation of the β-catenin-dependent signaling pathway. Due to the formation of a complex between ERα and β-catenin, the activity of the viral promoter was suppressed [31]. More recently, a direct inhibitory effect of E on SARS-CoV-2 infection was demonstrated *in vitro*. It became apparent that E2 can reduce the mRNA expression of the membrane-bound serine protease gene involved in the activation of the coronavirus spike protein [32].

Antiviral activity of estrogen-related medicines

L.M. Johansen et al. studied the antiviral effects of medications with activity in relation to E [33]. Several selective ER modulators (SERMs) were identified as potent inhibitors of *Zaire ebolavirus* infection. Blocking the entry of the virus is expected to occur due to a decrease in the level of cellular sphingosine and the subsequent accumulation of calcium [34]. Also, the antiviral activity of SERMs against other strains of the Ebola virus was discovered later. Subsequently, it was proposed to consider SERMs as antiviral agents due to their ability to interfere with the entry and replication of viruses, in particular, HIV and hepatitis C virus. The ability of SERMs to delay coronavirus infections (MERS-CoV and SARS-CoV-2) by inhibiting virus transmission at the late endosomal stage was discovered [20].

Conclusion

Based on the available literature, we conclude that biological sex differences may influence the mechanism of COVID-19 pathogenesis, the severity of the disease, and its biomarkers. Women are more protected from the development of a severe viral infection due to the formation of an effective innate and acquired immune response. Estrogens help them maintain their immune status during a viral infection. Current and future studies to decipher the effects of hormones on human physiology and immune responses have great potential to explain the heterogeneity of human pathogenic responses and may lead to more effective and personalized pharmacotherapy. In our opinion, current clinical trials for the prevention and treatment of COVID-19 must include gender-specific analyses.

Conflicts of interest

The authors declare no conflicts of interest.

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