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Potential Therapeutic Role of Estradiol Agonists and Androgen Antagonists in COVID-19

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Abstract

Epidemiological data from the COVID-19 pandemic shows increased severity and mortality among males compared with females. Several studies offer evidence that this disparity may be, in part, due to sex hormone biases contributing to different outcomes in SARS-CoV-2, suggesting hormone therapy as a potential combination treatment alongside antivirals in COVID-19. This review explores the potential mechanisms by which estrogen and androgen have distinct impacts on the development of COVID-19.

Keywords: COVID-19 • SARS-CoV-2 • Estrogen • Androgen • Antiandrogens • Cytokine storm • RAS • ACE2 • TMPRSS2

List of Abbreviations: COVID-19: Coronavirus Disease of 2019 • SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2 • ER: Estrogen Receptor • AR: Androgen Receptor • ACE2: Angiotensin-Converting Enzyme 2 • ACE: Angiotensin-Converting Enzyme • RAS: Renin-Angiotensin System • TMPRSS2: Transmembrane Protease Serine 2 • ADAM-17: A Disintegrin and Metalloprotease 17 • RAGE: Receptor for Advanced Glycation Endproducts • DHT: Dihydrotestosterone • GPER: G Protein-Coupled Estrogen Receptor 1 • HUVEC: Human Umbilical Vein Endothelial Cells • AT2R: Angiotensin II Type 2 Receptor • AT1R: Angiotensin II Type 1 Receptor • ARDS: Acute Respiratory Distress Syndrome • ROS: Reactive Oxygen Species • NF-κB: Nuclear Factor kappa-light-chain-enhancer of Activated B Cells • IL: Interleukin • TNF: Tumour Necrosis Factor • IFN: Interferon • CCL2: C–C motif Chemokine Ligand 2 • Th1: Type 1 T Helper • Th2: Type 2 T Helper • TGF: Transforming Growth Factor • FKN: Fractalkine • G-CSF Granulocyte Colony-stimulating Factor • HMGB1: High Mobility Group Box 1 • SERMS: Selective Estrogen Receptor Modulators

Background

Men account for 63% of hospitalizations and 57% of deaths due to the coronavirus disease of 2019 (COVID-19) worldwide, though incidence of infection does not differ greatly between the sexes [1]. There may be several possible explanations for this disparity between men and women, including comorbidities such as smoking and heart disease, X-linked chromosomal biases, and sex hormone biases [2,3]. This short review article will focus on the estrogen- and androgen-mediated responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and potential treatments alongside antivirals to combat SARS-CoV-2 infection.

The literature search was conducted through PubMed, Google Scholar, University of Toronto Libraries, and ClinicalTrials.gov using keywords including COVID-19, SARS-CoV-2, sex differences, hormonal effects, immune/inflammatory response, genomic regulation, viral entry, estrogen, estradiol, androgen, antiandrogen, estrogen/androgen receptor, Angiotensin-Converting Enzyme 2 (ACE2), Angiotensin-converting Enzyme (ACE), Renin-Angiotensin System (RAS), Transmembrane Protease, Serine 2 (TMPRSS2), Disintegrin and Metalloprotease 17 (ADAM-17), and the Receptor for Advanced Glycation Endproducts (RAGE).

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Estrogen Treatment in SARS-CoV-2 and SARS-CoV Infection

In vitro VERO-E6 cells, estradiol treatment reduced over 40% of SARS-CoV-2 viral load [4]. In a mouse model of SARS-CoV, ovariectomy and estrogen receptor blockers increased mortality [3]. A retrospective study found that for women above 50, those receiving estradiol therapy had an over 50% reduced fatality risk due to COVID-19 compared to those without [5]. A related class of drugs called Selective Estrogen Receptor Modulators (SERMs) is shown to have similar protective effects as endogenous estrogens by activating Estrogen Receptors (ER) in a tissue-specific manner [6]. This tissue-specificity, which is observed for both SERMs and endogenous estrogens, is believed to be the result of different expression of ER subtypes and co-regulators in different cell types, as well as different conformational changes caused by binding of different ligands, which ultimately result in transcriptional regulation of different gene targets [7,8]. For example, tamoxifen is being investigated in the context of COVID-19 and was found to increase protection against SARS-CoV in female mice [3]. This SERM demonstrates tissue-specific effects, acting as an estrogen antagonist in breast tissue and an agonist in the bone, uterus, and cardiovascular system [8]. Furthermore, many of these drugs, such as tamoxifen, clomiphene, and raloxifene, have additional, unique, ER-independent mechanisms that inhibit viral entry through interaction with viral glycoproteins or host proteins [9].

Antiandrogen Treatment in SARS-CoV-2 Infection

Antiandrogens are often achieved by blocking the AR and/or the production of androgens, the class of male sex hormones [10]. Both 5-α-reductase inhibitors (finasteride, dutasteride, enzalutamide) and AR-antagonists (bicalutamide, apalutamide, darolutamide, enzalutamide) have been tested *in vitro* for SARS-CoV-2. Finasteride and enzalutamide have been shown to reduce internalization of recombinant Spike protein into human alveolar epithelial cells and reduce SARS-CoV-2 titers in lung bud organoids [11,12]. Apalutamide, darolutamide, and enzalutamide dose-dependently reduced SARS-CoV-2 infection in LNCaP cells [13]. In contrast, Dihydrotestosterone (DHT), the natural agonist of the Androgen Receptor (AR), significantly increased uptake of recombinant Spike protein by human alveolar epithelial cells [11].

It has been reported that androgen deprivation therapy [14] and 5-α-reductase inhibitors, a class of antiandrogens that prevent conversion of testosterone into the more potent DHT [10], are associated with improved clinical outcomes in COVID-19 patients. A randomized clinical trial of proxalutamide, an AR-antagonist, has shown decreased hospitalization compared to a placebo group (2.2% *vs*. 26%) in male patients with COVID-19 [15,16]. Further studies by these authors suggest that proxaltumide and dutasteride treatment may reduce disease duration in COVID-19 patients also receiving standard of care by accelerating viral clearance and reducing inflammation compared with patients only receiving standard of care [17,18]. However, some scientists expressed concern regarding the strength of this association as patients receiving these antiandrogenic treatments often have abnormal hormonal regulation to begin with [19].

Potential Mechanisms by Which Estrogen Agonists and Androgen Antagonists Act

The sex hormones might influence viral infection and the inflammatory responses. Estrogen receptors (ER-α, and G protein-coupled estrogen receptor 1 (GPER)) are expressed in lung and cardiac tissues [20,21] as well as on immune cells. Once activated by their respective ligands, these receptors can act as transcription factors, forming complexes at genomic regulatory sites or mediating long-range chromatin interactions for a wide variety of genes [22].

The androgen receptor is also expressed in lung and cardiac tissue and on immune cells and can modulate expression of various genes [23,24].

Estrogenic Regulation of ACE2 and TMPRSS2

Estradiol's effect on ACE2 is reported differently in different cell types, decreasing mRNA expression in airway epithelial cells [25,26], but increasing mRNA expression and activity in cardiac cells [27], 2 adipose tissue [28], and human umbilical vein endothelial cells (HUVEC) [29]. This discrepancy might be due to tissue-specific effects of estrogen or different dosing procedures [30]. There is evidence that this regulation is mediated by ER- binding to the ACE2 promoter [27-29]. However, it is important to note that mRNA transcript levels are not always indicative of protein levels. In a study of HUVEC cells, Mompeon et al. found that estradiol increased ACE2 mRNA, but not protein levels. There is another possible post-transcriptional mechanism for the regulation of ACE2 protein by sex hormones. Shedding, which is believed to be a major regulatory mechanism for ACE2, is competitively mediated by the 'sheddase' ADAM-17 and TMPRSS2 [31], both of which are transcriptionally regulated by estrogen and androgen [32-35]. The effect of exogenous estradiol on ACE2 protein levels in comparison with mRNA needs to be examined in lung cells to better understand estrogen's potential impact on viral entry.

The relationship between estrogens and TMPRSS2 is less studied than that of androgens and TMPRSS2. Estradiol was found to downregulate TMPRSS2 mRNA in VERO E6 cells [4], MCF7 cells [36], and A549 lung epithelial cells [26]. However, ER-α and GPER expression were positively correlated with TMPRSS2 expression in atrial tissue [34]. As above, the effect of estrogen treatment on TMPRSS2 protein levels should be investigated in lung tissue.

Androgenic Regulation of ACE2 and TMPRSS2

Genomic and *in vitro* evidence suggest that endogenous androgens may aid viral entry through upregulation of both ACE2 and TMPRSS2, while antiandrogens may reverse this effect. Multiple AR binding sites were found upstream of the human ACE2 gene [37,38]. DHT was found to upregulate ACE2 protein expression in cardiac and alveolar epithelial cells [11], while antiandrogens have been shown to downregulate ACE2 mRNA and protein expression in stem cell-derived lung organoids and murine lungs [11,37-39].

There is significant evidence from prostate cancer research and emerging COVID-19 research for androgenic regulation of TMPRSS2 expression. AR can bind directly to the TMPRSS2 promoter and enhancer regions to increase transcription of the TMPRSS2 gene [38,40,41]. In A549 cells, testosterone upregulated both AR and TMPRSS2 expression and induced AR loading onto the TMPRSS2 promoter [23]. Antiandrogens, comparatively, have been shown to downregulate TMPRSS2 expression in lung epithelial and cardiac cells [11], as well as murine and hamster models [12,38,39]. Though Baratchain et al. found pulmonary TMPRSS2 expression to be unaffected in male mice. Overall, the research indicates that androgens, through activation of AR, can upregulate TMPRSS2 expression, potentially assisting viral entry, and antiandrogens may be able to reverse this effect.

In summary, the literature suggests that estrogen/ER may attenuate viral entry by downregulating TMPRSS2, while preventing loss of ACE2. However, further research is required to clarify the tissue-specific effects of estrogen. Androgen/AR can upregulate both ACE2 and TMPRSS2, while antiandrogens have the opposite effect (Figures 1 and 2).

ER- and AR-mediated Regulation of the RAS

A dynamic RAS response may be vital to clearance of pathogens and subsequent host recovery, with an initial decrease in pulmonary ACE2 to allow for pro-inflammatory signaling and neutrophil infiltration for viral clearance, followed by restoration of ACE2 levels to reduce vascular permeability and inflammation, thereby promoting tissue repair [42,43]. Overactivation of the proinflammatory, ACE/Ang II/

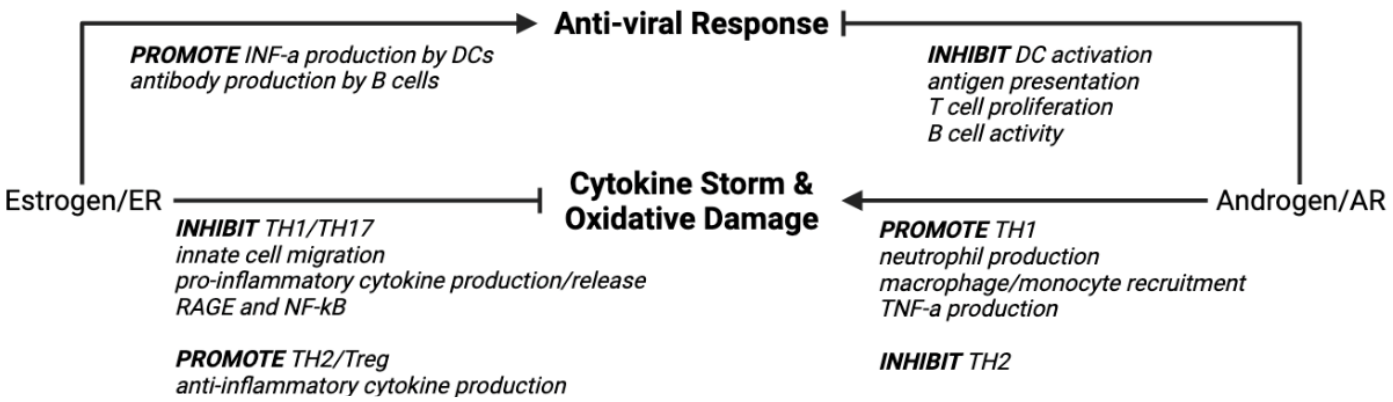

Figure 1. Proposed mechanisms for estrogenic and androgenic regulation of the immune response in the literature. AR (androgen receptor), ER (estrogen receptor), RAGE (receptor for advanced glycation endproducts), NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), TNF-a (tumour necrosis factor alpha), Th1 (type 1 T helper), Th2 (type 2 T helper), DC (dendritic cell), IL-6 (Interleukin 6). Created with BioRender.com

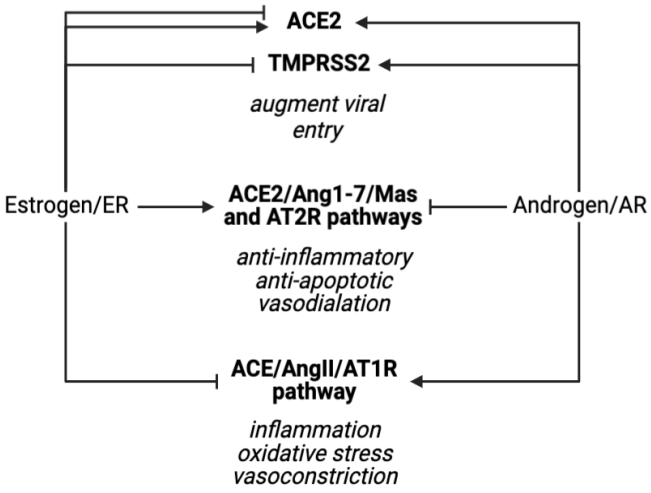

Figure 2. Proposed mechanisms for estrogenic and androgenic regulation of viral entry and RAS in the literature. AR (androgen receptor), ER (estrogen receptor), ACE (angiotensin-converting enzyme), ACE2 (angiotensin-converting enzyme 2), TMPRSS2 (transmembrane protease, serine 2), Ang (angiotensin), AT1R (angiotensin II receptor type 1), AT2R (angiotensin II receptor type 2). Created with BioRender.com

AT1R arm of RAS is associated with the cytokine storm and lung injury observed in the most severe COVID-19 patients [44]. Furthermore, vasoconstriction due to Ang II signaling could promote to thrombosis, another severe clinical manifestation of COVID-19 [45]. Androgenic and estrogenic regulation of RAS components may drive RAS towards or away from overactivation.

Estrogenic Regulation of RAS

Estrogen regulates, not only ACE2 but also other RAS elements, shifting the balance towards the ACE2/Ang1-7/Mas receptor and angiotensin II type 2 receptor (AT2R) pathways and away from the ACE/Ang II/AT1R pathway. This effect is suspected to contribute to gender biases in hypertensive diseases [46]. Estradiol was found to lower circulating Ang II in murine models [47] and increase Ang1-7 production in HUVEC cells [29]. Proposed mechanisms based on *in vivo* and murine studies include reduced expression/activity of ACE and angiotensin II type 1 receptor (AT1R), as well as increased expression/activity of AT2R, Mas, and ACE2. ER-α was implicated in some of the underlying mechanisms, though there are conflicting results between cell types regarding which combinations of these proteins within the pathway are and are not regulated by estrogen [27,29,46,48]. While the tissue-specific mechanisms are yet unclear, these results would suggest an overall anti-inflammatory, vasodilatory, and protective role for estrogen with respect to RAS.

Androgenic Regulation of RAS

The literature suggests that androgens have the opposite effect, shifting RAS towards the ACE/Ang II/AT1R arm and playing a permissive role in Ang II-mediated hypertension [49]. DHT was found to directly downregulate AT2R mRNA and protein expression in murine aortas through AR signaling *via* ERK1/2 MAP kinase [50]. Testosterone was also shown to upregulate AT1R mRNA in murine aortas [46,51], and renal tissue [52]. However, Hanson et al. challenged this, finding that castration of male mice increased mRNA expression of AT1R and ACE in the aorta and kidney, which was restored by testosterone treatment. Differences in dosage and procedure could account for this contradiction. Since androgens, like estrogens, can have tissue-specific effects, the interactions between AR/ER and the local RAS in the lungs need to be explored in greater depth.

In summary, the literature suggests overall that androgens support Ang II signaling by downregulating AT2R and upregulating AT1R, thereby promoting inflammation and vasoconstriction.

Estrogenic and Androgenic Modulation of the Inflammatory Responses

The cytokine storm triggered by COVID-19 infection consists of systemic overproduction of proinflammatory cytokines and severe endothelial inflammation. This process is believed to be a key contributor to the development of acute respiratory distress syndrome (ARDS) in the most severe COVID-19 patients. ER and AR are both expressed on various immune cells [6,24], allowing estrogen and androgen to interact with the immune system in a multitude of ways to modulate cytokine production and other aspects of the inflammatory response.

Estrogenic Regulation of the Immune Cell Interactions and Cytokine Production

The cytokine storm in COVID-19 patients is characterized by overproduction of proinflammatory cytokines, principally IL-6 and TNF-α, by immune cells in the Th1 effector response [53]. In a murine model of SARS-CoV infection, estradiol treatment was found to significantly attenuate this inflammatory response [3]. High concentrations of estrogen suppress neutrophil and monocyte migration and pro-inflammatory cytokine production by macrophages and monocytes and activate anti-inflammatory cytokine production by T-lymphocytes, thereby potentially offering protection against the cytokine storm [22,54,55]. Female immunity is skewed toward the Th2 and Treg responses over the Th1 and 17 responses [6,54]. However, female cells still exhibit higher immune reactivity than male cells [2,54]. Estrogen activates antibody production by B-lymphocytes, thereby promoting a strong adaptive immune response against viral infection, and activates INF- α production by dendritic cells, which is a key aspect of the innate antiviral defence [54]. Genomic regulation by ER-α, in particular, is thought to play a role in several of these pathways [2,6,56]. However, it is important to note that low concentrations of estrogen have been reported to have opposite effects, increasing pro-inflammatory cytokine production [22,54].

Estrogen Inhibits ROS Production *via* Inhibition of RAGE

Oxidative stress due to excessive Reactive Oxygen Species (ROS) production is commonly induced in viral infections and contributes to tissue damage and inflammation. Males with COVID-19 show enhanced oxidative stress compared with females [57]. There is evidence that estrogen modulates production of ROS *via* another mechanism, namely the RAGE. RAGE is a transmembrane receptor of the immunoglobulin superfamily that acts as a Pattern Recognition Receptor (PPR) in the innate immune response to viral infection. Infected cells and innate immune cells release the RAGE ligand, High Mobility Group Box 1 (HMGB1) [58]. Subsequent RAGE activation stimulates the pro-inflammatory response *via* NF-kB [58] and generation of ROS [59]. There is evidence that ER/estrogen inhibits the RAGE pathway and reduces oxidative stress, though the exact mechanism is not agreed upon [58]. This has been posited as another potential pathway for estrogen-mediated protection from tissue damage during SARS-CoV-2 infection [58].

Androgenic Regulation of Immune Cell Interactions and Cytokine Production

Androgens, comparatively, were found to have the opposite effect, suppressing Th2 while encouraging the Th1 effector response. In a hamster model of SARS-CoV-2, AR-antagonist, PT150-treated animals displayed decreased inflammatory cell infiltration and IL-6, with reduced tissue damage and viral load [39]. Androgens suppress the adaptive response through suppression of dendritic cell activation, antigen presentation to T-lymphocytes and their proliferation, and antibody production, thereby potentially increasing vulnerability to viral infection [2,24,54]. Meanwhile, androgens promote a strong innate immune response with inflammatory cytokine signaling by promoting neutrophil production, macrophage and monocyte recruitment, and TNF- α production by macrophages, potentially increasing risk of the cytokine storm [24]. Studies of COVID-19 patients showed higher proinflammatory cytokines, chemokines and endothelial injury markers in males compared with females [60]. AR has been implicated in the respective pathways for the generation/function of neutrophils, regulation of macrophage recruitment and pro-inflammatory cytokine production, and development/activation of T and B cells [24].

In summary, the female immune response appears to confer a stronger anti-viral response and greater protection against the cytokine storm compared with the male immune response, and regulation of immune pathways by sex hormone receptors is, in part, responsible for this difference.

Limitations

While the *in vitro* and *in vivo* studies discussed above demonstrate potential for antiandrogens and estradiol to attenuate viral infection *via* suppression of viral entry and the overactive inflammatory response leading to the cytokine storm, they only represent pieces of the puzzle. Questions remain regarding potential off-target effects of short-term hormone therapy and the significance of ER and AR-mediated regulation of viral entry and immune factors in the larger context of the human body's dynamic, multi-faceted response to SARS-CoV-2 infection. Both ERs and AR regulate a wide range of genes [22], and as such, upregulating or downregulating their activity through hormone treatment could have off-target effects. Furthermore, some authors have raised specific concerns regarding the use of 5-α reductase inhibitors, a class of antiandrogens that prevent conversion of testosterone into the more potent dihydrotestosterone. Androgen metabolism is speculated to play a role in restoration of the surfactant layer through modulation of communication between fibroblasts and lung epithelial cells, and as such, their use may in fact suppress healing from lung injury such as ARDS [61]. However, the exact mechanisms are poorly understood. Clinical trials of antiandrogens and estrogens currently underway will establish the effect of sex hormone therapies on the progression of COVID-19 infection and healing in the human body.

Conclusion

Sex biases in COVID-19 severity and mortality may be partially explained by hormonal regulation of viral entry, RAS, and immune factors by estrogen and androgen, largely through receptor-dependent pathways, though some receptor-independent pathways have been defined. Current research suggests estrogen receptor modulators and antiandrogens as potential attenuators of viral infection and COVID-19 pathologies associated with the cytokine storm, which could be delivered in conjunction with antiviral medications. However, given the numerous genes that are regulated by estrogen and androgen receptors and the widespread impacts of sex hormones on cellular and immune processes, which undergo their own dynamics under viral infection, it remains to be tested whether hormone treatments will offer a significant advantage to SARS-CoV-2 patients. Physicians and scientists are excited to look for the results of randomized, controlled clinical trials (NCT04853069, NCT04539626, NCT04865029, NCT04853134, NCT04853927) of antiandrogens and estrogen receptor modulators currently underway.

Competing Interests

The authors have no conflicts of interest to declare.

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Author's Contributions

M.S. conducted the literature search and drafted the text and figures. H.Z. perceived the presented idea and revised the manuscript and figures. All authors reviewed the manuscript and approved the final version.

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