Review Article
Role of Sex Steroid Hormones in Bacterial-Host Interactions

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Sex steroid hormones play important physiological roles in reproductive and nonreproductive tissues, including immune cells. These hormones exert their functions by binding to either specific intracellular receptors that act as ligand-dependent transcription factors or membrane receptors that stimulate several signal transduction pathways. The elevated susceptibility of males to bacterial infections can be related to the usually lower immune responses presented in males as compared to females. This dimorphic sex difference is mainly due to the differential modulation of the immune system by sex steroid hormones through the control of proinflammatory and anti-inflammatory cytokines expression, as well as Toll-like receptors (TLRs) expression and antibody production. Besides, sex hormones can also affect the metabolism, growth, or virulence of pathogenic bacteria. In turn, pathogenic, microbiota, and environmental bacteria are able to metabolize and degrade steroid hormones and their related compounds. All these data suggest that sex steroid hormones play a key role in the modulation of bacterial-host interactions.

1. Introduction

Sex steroid hormones such as progesterone, estradiol, and testosterone play a number of important physiological roles including reproduction, differentiation, development, cell proliferation, apoptosis, inflammation, metabolism, homeostasis, and brain function [1]. They are mainly synthesized by gonads, the adrenal gland, and the placenta and are released into the blood stream to act both in peripheral target tissues and the central nervous system [2]. Sex steroid hormones exert their function by binding to either specific intracellular receptors that act as ligand-dependent transcription factors (classical mechanism) or membrane receptors that stimulate several signal transduction pathways (nonclassical mechanism) [1, 3–5].

Interestingly, sex steroid hormones also participate in the communication between microorganisms and mammal hosts. This type of communication is commonly referred to as “interkingdom signaling” and can be used by microbial pathogens to activate their virulence factors and control the course and outcome of infection [6]. Notably, human and animal males, in general, are more susceptible to protozoan, fungal, bacterial, and viral infections than females [7]. This susceptibility could be due to the lower immune responses presented in males than in females, since innate responses, antibody-mediated, and cellular responses are typically lower in males than in females [7–9].

Numerous studies have reported the effects of sex steroid hormones on the dimorphic sex differences in the response to microbial and viral infections. In addition to affecting host immunity, sex hormones alter gene expression and behavior that influence susceptibility and resistance to infection [7]. This paper mainly focuses on the participation of sex hormones in the interaction between pathogenic bacteria and their hosts, their involvement in the host mechanisms used to minimize and eradicate the infection, as well as in the pathways used by bacteria to evade the immune response.

2. Mechanism of Action of Sex Steroid Hormones

Many actions of estradiol, progesterone, and testosterone are mediated by the classical or genomic mechanism of action
that involves specific intracellular receptors, ER, PR, and AR, respectively, which are members of the nuclear receptor superfamily of ligand-dependent transcription factors [11, 12]. Two PR isoforms have been reported in humans, which are encoded by the same gene but regulated by distinct promoters. These isoforms are PR-B of 114 kDa and an N-terminal truncated form, PR-A of 94 kDa [13]. There also exist two subtypes of ER, ER-α of 66 kDa and ER-β of 55 kDa, which are transcribed from different genes [14]. Similarly, there are two isoforms of AR encoded by a single gene, AR-A and AR-B; the latter has a molecular mass of 110 kDa, while the former has a molecular mass of 87 kDa and lacks the first 187 amino acids of the N-terminal region of AR-B [15].

Sex steroid receptors are modular proteins with distinct functional domains (Figure 1(a)). The N-terminal region contains the A/B domain that has the transcriptional activation function (AF)-1. The middle region (C domain) contains the DNA-binding domain (DBD) that is the highest conserved and the dimerization region. The C domain is followed by a hinge region (D-domain) that contains a
nuclear localization signal (NLS) and the binding sites for chaperone proteins that maintain receptors in an inactive state. The E domain contains the ligand-binding region (LBD), a second AF domain (AF-2) as well as a region for coregulators association. Finally, the F domain is located at the extreme C-terminal region and contains part of the AF-2 domain [10, 11, 16] (Figure 1(a)).

According to the classical model of steroid receptors action, in the absence of ligand, nuclear receptors are associated with the heat-shock proteins Hsp70 and Hsp90. When the hormone interacts with its specific intracellular receptor, it induces conformational changes that allow dissociation of Hsp70 and Hsp90 promoting dimerization, phosphorylation, and high affinity binding to hormone response elements (HREs) located in the promoter region of target genes. Then, receptors modulate transcription by recruiting components of the basal transcriptional machinery. Sex hormone receptors also mediate transcriptional activity by recruiting a group of coactivator and adapter proteins, which function as acetyl transferases, ligases, ATPases, methylases, cell cycle regulators, RNA helicases, and docking proteins to bridge to basal transcription factors. In addition to coactivators, several corepressors have been characterized that activate a family of histone deacetylases, which activity results in failure to recruit the basal transcription machinery and inhibition of gene expression [5, 11] (Figure 1(b)).

Besides the classical mechanism of action, sex steroids can act in the cells through the nonclassical or nongenomic mechanism of action, in most cases mediated by membrane receptors. Thus, membrane progesterone receptors (mPRs) have been identified. Progesterone induces rapid responses in target cells such as spermatozoids, neurons, myometrial cells and immune cells through interaction with its mPRs, and mediates signaling via G-protein-coupled pathways [17]. Estradiol can associate with the transmembrane G-protein-coupled estrogen receptor-1 (GPR30) activating the trimeric G-protein. GPR30 plays an important role in the cardiovascular and immunological systems [18, 19]. G-protein-coupled receptors for androgens have also been identified in several cell types, including breast and prostate tumor cells, vascular and immune cells [20] (Figure 1(b)).

The signaling pathways of the nongenomic actions of sex steroids involve ion channels, enzyme-linked receptors, cyclic AMP and cyclic GMP production, mitogen-activated protein kinases (MAPKs), tyrosine kinases, and lipid kinases cascades (Figure 1(b)) [21–24]. Thus, progesterone modifies calcium influx in spermatozoa by opening membrane Ca\textsuperscript{2+} channels and activating the Src/p21\textsuperscript{ras} /ERK kinase pathway. Besides, progesterone can activate MAPK pathway in different cell types [21, 25, 26]. Testosterone can depolarize Sertoli cells and cause calcium influx through inhibition of K+ ATP channels; this hormone can also activate MAPK cascades through activation of the kinases Ras, Raf, MEK (mitogen-activated protein kinase/ERK kinase), and ERK (extracellular-signal-regulated kinase) [27]. In the case of estradiol, it can interact with GPRs in vascular cells, which activate the Src kinase that phosphorylates the epidermal growth factor receptor (EGFR) and releases metalloproteases, which trigger the release of EGF ligand from heparin. Then, EGF binds to EGFR, activating the Ras/Raf/MEK/ERK kinase system [11].

3. Modulation of Immune Responses by Sex Steroid Hormones

Sex steroid hormones markedly regulate the activity of immune cells, including lymphocytes, macrophages, granulocytes, and mast cells. The modulation of the immune system by sex steroids has both physiological and pathological implications [8, 9].

Androgen receptors have been identified in various lymphoid tissues, including the thymus and bone marrow, as well as in the spleen and in macrophages [8]. It has been reported that testosterone reduces natural killer (NK) cell activity in mice [28] and the synthesis of proinflammatory cytokines, including the tumor necrosis factor-alpha (TNF\textalpha) through the inhibition of transcriptional factors such as the nuclear factor kappa B (NF\textkappaB) [29], whereas this hormone increases the synthesis of anti-inflammatory cytokines such as interleukin 10 (IL-10) [30]. Testosterone also decreases the expression of macrophage and monocyte Toll-like receptor 4 (TLR4), which is grouped in a family of pattern recognition receptors (PRRs) and is involved in the activation of the innate immune system in response to pathogen challenge [31].

On the other hand, estrogens can enhance cell-mediated and humoral immune responses. ERs are expressed in various lymphoid tissue cells as well as in circulating lymphocytes and macrophages [8]. Estradiol contributes to resistance against infections by enhancing NK cell cytotoxicity and stimulating the synthesis of proinflammatory cytokines such as IL-1, IL-6, and TNF\textalpha [32, 33]. Estradiol also inhibits the production of IL-4, IL-10, transforming growth factor beta (TGF-\beta) and interferon gamma (IFN-\gamma) [34, 35]. Additionally, estrogens may protect immune cells against apoptosis [36].

PRs have been identified in epithelial cells, mast cells, granulocytes, macrophages, and lymphocytes [8]. Progesterone is typically known as an immunosuppressive agent since it inhibits the activation of NF\textkappaB and increases the expression of the suppressor of cytokine signaling protein (SOCS1) in macrophages [37]. Progesterone also reduces macrophage and NK cell activity [33, 38, 39] as well as antibody production by B cells [40]. Elevated concentrations of progesterone during pregnancy inhibit the development of Th1 (helper T-cell immune type 1) responses and the production of proinflammatory cytokines such as IFN-\gamma, while promoting Th2 immune responses, including the synthesis of anti-inflammatory cytokines such as IL-4, IL-5, and IL-10 [41].

4. Effects of Sex Steroid Hormones on Bacterial Infections

Different studies provide evidence that males exhibit greater susceptibility to bacterial challenge than their female counterparts [42]. Experimental models of infection in castrated
animals with or without hormonal substitution have been used to study the role of sex hormones in bacterial infections [43].

An approximation to determine the effects of sex hormones over bacterial infection has been the endotoxin lipopolysaccharide (LPS) administration to experimental animals to reproduce sepsis. Sepsis is driven by the overproduction of cytokines such as TNF-α, IL-1β, and IL-6 by macrophages, which detect bacteria and endotoxins via TLRs [44]. Circulating levels of these cytokines are higher in sepsis male patients and mice than their female equivalents, while levels of IL-10 are higher in female than in male patients or male mice treated with LPS [45, 46]. There is evidence that estradiol administration increases survival by decreasing the oxidative stress along the rat gastrointestinal tract following intraperitoneal LPS challenge [47]. In line with this observation, the removal of endogenous estrogens following ovariectomy increases mortality associated with LPS challenge in rats, and this effect was reverted by estrogens treatment. Besides, androgenized females have a higher rate of mortality following LPS administration [48].

Mycobacterial infections occur more frequently in males than in females. This is the case of *Mycobacterium tuberculosis* that produces a higher number of tuberculosis cases in men in all regions of the world, phenomenon that may involve sex hormones [49]. Male mice infected with *M. marinum* are more susceptible than females to mortality and bacterial colonization of lungs and spleen. When exogenous testosterone is administered, the susceptibility of female mice to infection increases, whereas castration in males attenuates the infection, demonstrating that testosterone is responsible for the increased susceptibility to *M. marinum* infection [50].

It has been demonstrated that estradiol and progesterone alter the gastric mucosal response to early *H. pylori* infection in ovariectomized gerbils, modifying the mucosa turnover. Progesterone-treated gerbils presented less gastritis, and a synthetic progesterone derivative (17-α-hydroxyprogesterone caproate) impairs the viability of *H. pylori* [51].

Another example of predisposition to infections in males is seen during Q fever, a zoonotic infection caused by *Coxiella burnetii*, which is considered a potential biological weapon. Men show symptoms, such as flu-like syndrome, pneumonia, hepatitis, myocarditis, pericarditis, meningitis, or encephalitis, more often than women. When mice were infected with *C. burnetii*, it was observed that bacterial load and granuloma number in spleen were higher in males than in females. Ovariectomized mice showed increased bacterial load in the spleen and liver, whereas the treatment of ovariectomized mice with estradiol reduced it [52].

Sex steroid hormone effects on diseases produced by bacteria depend on the infective species and sex steroid hormone levels. In contrast with the data presented above, there are bacterial infections with major incidence in women and female animal models. For example, in mice infected with *Pseudomonas aeruginosa*, indicators such as weight loss, bacterial load, and inflammatory mediators in the lung were higher in females than in males, suggesting a possible role of estrogens in female predisposition to infection by *P. aeruginosa* [53]. In support of this hypothesis, it has been observed that the administration of estradiol to male mice with pneumonia caused by *P. aeruginosa* leads to more severe inflammation in lung tissue and an increased expression of IL-17 and IL-23 [54].

It has been reported that female propensity to typhoid infection is due to estrogens, since the treatment with estradiol increases female mice susceptibility to an intraperitoneal *Salmonella typhimurium* challenge, whereas the treatment with progesterone increases the resistance to the infection and the survival time, suggesting a differential role of ovarian sex hormones in this infection [55]. Pregnant mice infected with *S. enterica* serovar Typhimurium showed a higher bacterial load in the spleen than nonpregnant mice, which correlates with a diminished splenic recruitment of dendritic cells, neutrophils, and NK cells, a decrease in IL-12 production, and increased levels of IL-6 [56].

Another example is the susceptibility of women to *Listeria monocytogenes* infection during pregnancy when estradiol and progesterone levels are very high [42]. Also during pregnancy, gingivitis and pyogenic granuloma have been related for the increased susceptibility to *Listeria monocytogenes* infection during pregnancy when estradiol and progesterone, which in turn enhance bacterial growth. Additionally, these sex hormones can act as substitutes for vitamin K, an essential growth factor for *P. intermedius* [59].

It has also been demonstrated that progesterone (32–127 μM) inhibits the growth of *Neisseria gonorrhoeae* and *N. meningitidis*. This effect was either bacteriostatic or bactericidal, depending on progesterone concentration [61]. Interestingly, it has been shown that during infection of primary cervical epithelial cells, the treatment with progesterone (30 nM) increases *N. gonorrhoeae* survival and replication through subversion of the activity of the host serine-threonine kinase Akt by the gonococcal phospholipase D [62]. This opposite effect of progesterone could be due to the different doses of the hormone used in each study.

Studies using mouse, rat, and guinea pig models of genital tract *C. trachomatis* infection suggest that the hormonal status of the genital tract epithelium influences the outcome of the *Chlamydia trachomatis* infection [63]. In an in vitro model of infection of HeLa cells with *C. trachomatis*, estradiol preexposition of cells enhances the adherence of chlamydial elementary bodies, as well as the development of bacterial inclusions [64]. Recently, it was demonstrated that the
5. Bacterial Metabolism of Sex Steroid Hormones

Bacteria are capable of metabolizing sex steroid hormones through the activity of distinct enzymes such as hydroxysteroid dehydrogenase (HSD) that regulate the balance between active and inactive steroids. Bioinformatics analyses have identified genes that encode HSDs in distinct bacterial genomes. The dominating phyla that were identified to express these enzymes were Actinobacteria, Proteobacteria, and Firmicutes. A large number of HSD-expressing bacteria constitute the normal gastrointestinal microbiota, while another group of bacteria were isolated from natural habitats like seawater, soil, and marine sediments [67].

In regard to pathogenic bacteria, Prevotella intermedia (previously Bacteroides melaninogenicus subsp. intermedia), a gingival infective agent, upakes progesterone and estradiol [59], while Streptococcus mutans and Bacillus cereus metabolize testosterone and progesterone due to the activity of 5α-steroid reductase 3β-, 17β-, and 20α-HSDs [68]. Porphyromonas gingivalis and Actinobacillus actinomycetemcomitans also reduce testosterone to 5α-dihydrotestosterone [69].

Treponema denticola, another gingival bacterium associated with periodontitis, metabolizes cholesterol, progesterone, and testosterone using 5α-reductase, 3β- and 17β-HSD activity [70]. However, only cholesterol induces bacterial growth, whereas high concentrations of progesterone and testosterone inhibit it. The lack of sensitivity of T. denticola to low concentrations of progesterone and testosterone (0.0001 μg/mL) may be due to their active removal by an ATP-binding cassette (ABC) efflux transporter [71].

It has been reported that sex steroid hormones are substrates of E. coli multidrug efflux (MDE) pumps that are important factors in the resistance against bile acids. Two of these MDE systems, AcrAB-TolC and EmrAB-TolC, can transport estradiol and progesterone outside the bacterial cell. Additionally, when both systems were mutated, a steroid hormone-dependent growth suppression was observed [72]. Likewise, in N. gonorrhoeae, it has been demonstrated the participation of an efflux pump (MtrCDE) in the transport of sex hormones, which concerns bacterial resistance to progesterone [73]. Efflux-deficient gonococcal mutants were more rapidly cleared from infected intact female mice than from ovariectomized mice and were more sensitive to progesterone in vitro [73]. These pumps may be essential for bacterial survival under conditions where steroids are present, such as in the gastrointestinal, vaginal, and urinary tracts [72].

Pathogenic bacteria also have an influence over host sex hormone metabolism. For instance, S. enterica infection in a murine model reduces the levels of steroid hormones such as progesterone. The analysis of the transcript levels of genes that encode several enzymes involved in the synthesis of steroid hormones reveals that the expression of some HSDs is reduced [74].

In addition to bacterial pathogens, bacteria from human microbiota play an important role in the metabolism of sex hormones. Microbiota is critical for human health since it has been implicated in the development of immune system, energy homeostasis, and protection against pathogens. Moreover, imbalances in the intestinal microbiota have also been associated with pathological processes [75]. A known cause of intestinal microbiota alteration is the use of antibiotics that can increase the susceptibility to enteric infections [76]. In a recent metabolic study, it has been determined that the treatment of mice with streptomycin disrupts the intestinal homeostasis, through a reduction in the number of fecal bacteria and consequently by affecting the intestinal metaboloma. 87% of all metabolites detected were diminished, including steroids, suggesting that the intestinal microbiota is involved in steroid metabolism [75].

It has been observed that fecal bacteria can perform hydrolytic, reductive, and oxidative reactions of androgens and estrogens [77]. Enzymes involved in 21-dehydroxylation or 16α-dehydroxylation of steroids such as corticosteroids and sex hormones have been identified in intestinal microbiota, and interestingly, these enzymes are not present in mammalian tissues [78]. Reversible 17β reduction of androgens carried out by human intestinal microorganisms is
suggest to play a role in the regulation of testosterone levels and in the release of androgens in humans [78, 79].

Sex-steroid metabolism is not only carried out by pathogenic or microbiota bacteria, but also by environmental bacteria, such as soil-, marine-, and sludge-associated organisms. The most studied example of steroid metabolism and steroid-dependent gene regulation in bacteria is the soil bacterium Comamonas testosteroni (formerly Pseudomonas testosteroni) [80]. C. testosteroni expresses various genes that respond to steroids including receptors such as TeiR, as well as activators (TesR) and repressors (RepA and RepB) of the 3α-HSD/carbonil reductase (CR)-encoding gene, hsdA. These proteins participate in the adaptation of the bacterium to the environment [81, 82]. Particularly, 3α-HSD/CR is an enzyme involved in the metabolism of androgens that mediates the oxide reduction of androstenedione, 5α-dihydrotestosterone, and androsterone. Interestingly, the expression of 3α-HSD/CR is highly inducible in the presence of steroid substrates [67, 83].

A testosterone catabolic pathway that differs to that found in C. testosteroni has been described in Steroidobacter denitrificans [84], a bacterium isolated from sludge that is capable of metabolizing estradiol and testosterone [85]. This bacterium oxidizes testosterone to 1-dehydrotestosterone, which is then transformed into androsta-1,4-diene-3,17-dione that in turn undergoes a reduction reaction occurring at its A ring; probably this reaction is accomplished by an as yet unidentified 3α-HSD [84]. Some seawater bacteria can also degrade steroids, for instance the marine bacterium H5, belonging to the genus Vibrio, can degrade testosterone and estrogens. Additionally, two estradiol inducible genes coding a 3-ketosteroid-Δ1-dehydrogenase and a carboxylesterase were identified [86].

Since natural and synthetic steroid hormones released into the environment are a potential health risk to humans and animals by interfering with sexual development and reproduction, among other functions, steroid-degrading bacterial species may be useful in the bioremediation of
contaminated environments, process also known as bioaugmentation [67]. The latter has been successfully applied in a variety of environments and in degradation of different pollutants such as petroleum hydrocarbon, phenol, and the herbicide atrazine [87]. Estradiol and its primary degradation product estrone have been detected in surface water, groundwater, livestock, and municipal wastes. The majority of bacteria that degrade estradiol such as Bacillus amylovorans, B. subtilis, and B. cereus have been isolated from sludge and can convert estradiol into estrone, but they cannot further degrade estrone [88]. Other estradiol-degrading bacteria isolated from activated sludge of a wastewater treatment plant that can be used in bioremediation of polluted environments correspond to genera Aminobacter, Brevundimonas, Escherichia, Flavobacterium, Microbacterium, Nocardioes, Rhodococcus, and Sphingomonas. Most of these strains cannot further degrade estrone [89].

In Stenotrophomonas maltophilia, a bacterium that degrades estradiol, it was determined that estrone is converted into tyrosine through the cleavage of its saturated ring, this amino acid in turn can be utilized in protein biosynthesis; however, the enzyme responsible of this conversion was not identified [90]. Sphingomonas strain KC8, whose genome sequence has been recently reported [91], has the capability of degrading different steroids, such as estradiol, estrone, and testosterone [92]. Although the degradation mechanism used by this bacterium has not been identified, its genome contains several genes encoding the enzymes putatively involved in estrogen degradation, such as HSD, 3-ketosteroid-Δ1-dehydrogenase and catechol 2,3-dioxygenase [91]. Another bacterium of the Sphingomonadaceae family, named EDB-L11, forms biofilms and it also degrades estrone [87].

The identification of key enzymes in biodegradation could help to discover microbial estrogen degradation pathways and suggest biomarkers to monitor estrogen degradation by a microbial community [90], which can be constituted by a mixture of distinct bacteria capable of degrading various classes of steroid hormones and their related compounds.

6. Conclusions

Sex steroid hormones play important roles in diverse functions of mammals, such as the modulation of the immune response. Testosterone, estradiol, and progesterone can differentially regulate responses against bacterial infections and alter metabolic pathways of pathogenic and microbiota bacteria. In general, testosterone acts as an immunosupressor, while estradiol acts as an activator, and progesterone acts as a modulator of the immune system. These effects are related to the sexual dimorphism found in bacterial infections, where men and male animals are in many cases more susceptible to bacterial infections than females. The stage of the menstrual or estrous cycles and pregnancy also determines the outcome of bacterial infections due to the changes in the levels of sex hormones. In some cases, administration of sex hormones may control the course of bacterial infections, functioning as a complement to antibiotic therapy. In turn, bacteria have developed mechanisms to eliminate or to exploit sex hormones in their benefit by using them as carbon and energy sources, principally through their degradation or chemical modification. Interestingly, this feature can be utilized in human benefit by using bacteria capable of degrading and eliminating steroid hormones from polluted environments. The knowledge of the specific enzymes and mechanisms involved in these processes could be helpful in the selection of appropriate bacteria to be used in bioremediation programs.

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