The impact of sex and sex hormones on lung physiology and disease: lessons from animal studies


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**Running head:** Sex and sex hormone effects on the lung

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Abstract

Numerous animal studies have revealed significant effects of sex and sex hormones on normal lung development, lung physiology and various lung diseases. The primary goal of this review is to summarize knowledge to date on the effects of sex and sex hormones on lung development, physiology and disease in animals. Specific emphasis will be placed on fibrosis, allergic airway disease, acute lung injury models, respiratory infection and lung toxicology studies.

**Keywords:** Estrogen, androgen, pulmonary.
Introduction

Several animal models have been used to study lung development, physiology and pathophysiology, and many of these studies have revealed sexual dimorphism in various aspects of these processes. As animal models are a critical component in the understanding of human lung biology and disease, and in the development of therapies, it is important to understand the effects that sex hormones and sex have on lung physiology and disease, and the mechanisms involved. Sex differences in the lung may be present because of developmental differences and/or may be due to the effects of prevailing levels of male and/or female sex hormones.

Steroid hormones and metabolism

Steroid hormones are synthesized primarily in the gonads, adrenal glands and the feto-placental unit. Cholesterol, which is the common precursor of all steroid hormones, is first converted to pregnenolone and the steroidogenic pathway then diverges towards the formation of sex hormones, glucocorticoids or mineralocorticoids. In the sex hormone pathway, pregnenolone is first converted to progesterone which serves as an intermediate for the synthesis of androgens and estrogens (Figure 1) (53). Estrogens are synthesized from androgens by the formation of an aromatic A ring and this reaction is catalyzed by the enzyme aromatase (46, 53). Sex steroid hormones act via their receptors: estrogen via estrogen receptor (ER) α or ERβ, progesterone via progesterone receptor (PR)-A or PR-B and androgens via the androgen receptor (AR) (26, 36, 46). Simplistically speaking, ligand bound sex steroid hormones receptors dimerize and bind to specific DNA response elements to modulate transcription (46). In recent years, newer concepts of sex steroid hormone receptor signaling have emerged including rapid cellular activation pathways that do not involve direct alteration of gene transcription (46).
Importantly, all sex steroid hormone receptors have been shown to be expressed in lung tissue (12, 20, 32, 49, 73, 89) and will be discussed in more detail in later sections.

**Lung development**

It is well established in many species that lung maturation, as measured by surfactant production, is delayed in male fetuses compared to female fetuses (50, 78, 79). Several studies suggest that the presence of higher levels of androgens in male fetuses underlie this sex difference. In the rabbit, administration of androgens to pregnant dams delays fetal lung maturation whereas administration of the anti-androgen flutamide abolishes the sex difference in lung maturation by increasing male surfactant levels to those of females (51). Androgen receptors, which mediate androgen effects, are present in both male and female lungs (20, 73), and in the developing lung there is active androgen metabolism where androgen synthesis and inactivation take place (55-57). In the mouse, many of the genes involved in androgen metabolism are regulated specifically on gestational day 17.5 which coincides with the emergence of mature alveolar type II cells which are responsible for surfactant biosynthesis (58). Synthesis and inactivation of 5α-dihydrotestosterone, the most potent androgen, occur through 5α-reductase and 3α-hydroxysteroid dehydrogenase (HSD) activity respectively. Provost and Tremblay recently showed that expression of 3α-HSD increases markedly on gestational day 17.5 when the maturation of alveolar type II cells occur and their results suggest that 3α-HSD RNA could be a reliable marker of lung maturity in fetuses (58). Dammann and co-workers investigated some of the signaling pathways involved in androgen regulation of fetal mouse lung development. They found that chronic androgen treatment downregulates epidermal growth factor receptor activity and upregulates transforming growth factor-β receptor activity leading to
an inhibition of surfactant protein gene expression in alveolar type II cells (14). Sex differences in alveolar type II cell maturation are also associated with differential expression of a variety of other genes relevant to development and surfactant production, including genes encoding apolipoproteins that are involved in lipid transport (67).

While the role of androgens in lung maturation has received much attention, less is known about the role of estrogens in this process. Fetal plasma levels of estrogen are in abundance in the latter stages of gestation in many species (9, 18, 61). Maternal administration of estrogen accelerates lung maturation and stimulates surfactant production in the fetal rabbit and rat (21, 29-31, 54). In newborn piglets, prenatal estrogen deprivation significantly impairs alveolar formation and fluid clearance (81).

The chloride channel cystic fibrosis transmembrane conductance regulator (CFTR) and the epithelial sodium channel (ENaC) are important in lung development. The ENaC plays a critical role in the active reabsorption of alveolar fluid during pulmonary edema (43) and at birth, a process which is critical for the switch from placental to pulmonary delivery of O₂ (28). CFTR is known to regulate other ion channels including ENaC (72) and is thought to be important in the differentiation of the respiratory epithelium during development (5). Sexually mature female rats have higher levels of mRNAs encoding α-ENaC and CFTR relative to males (74). Combined, but not separate, administration of progesterone and estradiol augments mRNA levels of rENaC subunits or CFTR in sexually immature female rats (74). The authors concluded that increased expression of ENaC in female lungs may confer an advantage to females in better clearance of fetal lung liquid at birth or during pulmonary edema (74).

At the onset of sexual maturity, virgin female rats and mice have higher body mass specific gas-exchange surface area (Sa) and smaller alveoli than age-matched males, although
there is no difference in mass-specific oxygen consumption (42). The authors speculated that the differences in Sa and alveolar size may have been selected for evolutionarily to help females meet the metabolic and O_{2} demands of reproduction (42). It was subsequently determined that estrogen is responsible for the sexual dimorphism in Sa and alveolar size (41). At 59 days, rats ovariectomized on day 21, have smaller Sa and larger alveoli than sham ovariectomized rats (41). Female rats treated with estrogen have smaller and more alveoli than females not receiving estrogen (41). Androgenization of newborn female rats has no effect on Sa or alveolar size and similarly, androgen receptor deficient mice have the same Sa as their wild type littermates (41), thus ruling out the involvement of androgens in this particular process. In mice, estrogen is also required for the maintenance of already formed alveoli and induces alveolar regeneration after their loss in adult ovariectomized mice (40).

Estrogens exert most of their effects through estrogen receptors (ERs) α or β. Both receptors are present in the lung with ERβ being more abundant than ERα (12). By examining estrogen receptor deficient (ERKO) mice, it was determined that both ERα and ERβ are required for the formation of a full complement of alveoli in female mice, that ERα mediates the sexual dimorphism of body mass specific alveolar number and surface area, and that absence of ERβ diminishes lung elastic tissue recoil (39, 40). In male mice, estrogen receptors have a smaller effect on alveolar dimensions than in female mice (39). Patrone et al. investigated the alveolar defects in more detail and found deficiencies in platelet derived growth factor A (PDGF-A) and granulocyte-macrophage colony-stimulation factor (GM-CSF) in the lungs of adult βERKO mice (52). Since both PDGF-A and GM-CSF are critical factors in alveolar formation and surfactant production, and are controlled at the transcriptional level by ERβ, the authors concluded that the
alveolar defects in the βERKO mice could be due to modifications in the expression of PDGF-A and GM-CSF (52).

**Lung and airway physiology**

Sex differences in certain aspects of lung function in experimental animals have been documented. We recently found that male mice have increased tidal volume and peak inspiratory flow rates compared to female mice (8). Total lung capacity and enhanced pause (Penh), a non-invasive measure of bronchoconstriction, have been reported to differ in naïve male and female mice, with males demonstrating greater enhanced pause responses to inhaled methacholine and possessing larger lungs than females (8, 59). However, it should be noted that doubt has been cast on the validity of the Penh measurement (3). Conversely, although a detailed morphometric analysis has not been reported, the conducting airways of female mice have been proposed to be larger than those of males (59).

There are several examples in the literature of the effects of sex and sex hormones on the control of breathing in animals. One study showed that conscious adult female rats have a greater hyperventilatory response to hypoxia than males, an effect that did not appear to be mediated by ovarian hormones as the effect was still present in ovariectomized females and in prepubertal rats (48). In the male rat, combined administration of a synthetic potent progestin and estradiol for 5 days significantly increased tidal volume and minute expiratory ventilation, reduced arterial PCO₂, and enhanced the ventilatory response to CO₂ inhalation (75). In mice of the OF1 strain, males were less resistant than females to a normobaric hypoxia and treatment of castrated males or ovariectomized females with estradiol increased hypoxic survival (71). Studies in swine showed that females are better able to adjust to hypobaria (44).
The estrogen receptors ERα and ERβ, and the AR, are expressed in respiratory motor neurons (4). An ERα antisense vector decreased brain ER levels and affected ventilation in male and female rats (27). Interestingly, we found a marked reduction in breathing frequency in male and female αERKO mice relative to wild type controls (8). As mentioned earlier, tidal volume was significantly increased in male wild type mice compared to female wild type mice; however, this pattern was reversed in αERKO mice (8). Similarly, minute ventilation, peak inspiratory flow, and peak expiratory flow were higher in male versus female wild type but not in αERKO mice (8). Together, these data indicate that functional disruption of ERα leads to changes in a variety of respiratory parameters and suggest that this nuclear receptor may be a critical regulator of breathing and respiratory rhythmogenesis in mice. ERβ disruption had no influence on sex differences in tidal volume, minute ventilation, peak inspiratory flow and peak expiratory flow (8). However, breathing frequency was significantly lower and peak inspiratory flow was significantly higher in female βERKO relative to female wild type mice (8). Tidal volume was higher in both male and female βERKO mice relative to their respective wild type controls (8). Consistent with this observation, as discussed in the previous section, Massaro and Massaro reported that βERKO mice have a higher body mass-specific lung volume relative to wild type mice (40).

**Fibrosis and other interstitial lung diseases**

A variety of animal models have been used to study idiopathic pulmonary fibrosis and other interstitial lung diseases, and some sex related effects have been observed. Chronic exposure of mice to cigarette smoke can lead to the development of emphysematous-like changes in alveolar structure and related alterations of pulmonary function, and these changes
develop more rapidly in females compared to males (37). Following bleomycin treatment, female rats exhibited higher mortality rates and more severe fibrosis than males, as indicated by higher levels of lung collagen deposition and fibrogenic cytokine expression (19). Ovariectomy diminished fibrosis whereas estradiol replacement restored the fibrotic response to that of the intact females. Furthermore, estradiol had a direct fibrogenic effect on rat lung fibroblasts mediated by increased expression of procollagen 1 and TGF-β1 mRNA expression in lung fibroblasts (19).

In contrast to rats, bleomycin treatment of mice leads to a greater degree of fibrosis in males versus females, as determined by histological assessment (23). This study suggested that one potential mechanism for the sex disparity is differential expression and/or activity of bleomycin hydrolase in the lungs of male and female mice (23). We have recently observed that male C57BL/6 mice display greater declines in static compliance than female mice following bleomycin treatment (Voltz, Card, Carey and Zeldin, unpublished observation). Whether these observations are the result of androgenic, estrogenic or a combination of sex hormone effects remains to be determined. Interestingly, Markova and colleagues reported that naïve, adult male C57BL/6 mice (16 weeks of age) had approximately 25% more lung hydroxyproline, a measure of collagen content, than age-matched females (38). This increased level of lung collagen was not present in male mice deficient in the AR (Ar<sup>Tfm</sup>), indicating a contribution of the AR pathway to the observed male-female differences in lung collagen levels (38). Lekgabe and colleagues recently demonstrated an interesting synergism between the hormones relaxin and estrogen in the development of pulmonary fibrosis (34). They found that airway fibrosis is under the influence of both relaxin and estrogen and that estrogen can partially protect the lung from disease progression in the absence of relaxin (34).
Allergic airway disease

Several studies have reported an increased susceptibility to allergic airway disease in female mice compared to male mice (11, 24, 45, 64). Corteling and Trifilieff reported increased serum IgE in allergic female mice compared to male mice and that female mice were less sensitive to the therapeutic effects of the steroid budesonide (11). Similarly, Seymour et al., reported significantly greater levels of total and OVA-specific IgG1 and IgE in the serum of allergic females compared to allergic males (64). Hayashi and colleagues reported less severe bronchial-bronchiolar inflammation in allergic males compared to allergic females (24). Following castration, males were similar to females suggesting a protective role for androgens in the development of allergic airway disease (24). Ovariectomized rats developed less airway inflammation compared to sham controls (35). Estrogen replacement in ovariectomized rats re-established airway inflammation to levels found in intact females (35). Treatment of female rats with the ER antagonist tamoxifen also blunted the development of allergic airway disease (35). In addition, administration of exogenous progesterone accentuated allergic airway disease in mice (25). The findings of a recent study by Melgert et al offer a potential mechanism for increased sensitivity in females (45). In that study, the authors found that control female mice had significantly fewer naturally occurring regulatory T (Treg) cells in their lungs compared to male controls. Treg cells are thought to play an important role in controlling Th2-biased responses and allergic diseases have been associated with impaired function of this cell type (84). Melgert and co-workers proposed that the reduction in Treg cells in female mice may indicate that they are less protected against inflammatory stimuli such as an allergen, compared to males (45). It would be of interest to determine what effect ovariectomy and hormone supplementation would have on the levels of these regulatory cells in the lung. Inhalation of
environmental tobacco smoke has been shown to aggravate the allergic response (62, 65). Female mice are much more susceptible than males to the influence of environmental tobacco smoke on the allergic response (64), and progesterone and environmental tobacco smoke act synergistically to exacerbate allergic airway disease in mice (47).

Airway hyperresponsiveness (AHR) to cholinergic agents is a defining feature of asthma. Cholinergic airway responsiveness is markedly different in male and female mice (6, 7). Males of the C57BL/6 and BALB/c strains are more sensitive than females to inhaled methacholine as determined by greater changes in total respiratory system resistance, elastance and other mechanical parameters (6). We recently reported that this sex difference appears to be due to in vivo effects of androgens on vagus nerve-mediated reflex pathways and not to differences in innate responsiveness of airway smooth muscle (7). The effects of estrogen on cholinergic responsiveness have also been studied. In rats, estradiol treatment decreased acetylcholine induced airway reactivity in part by increasing epithelial acetylcholinesterase activity (15). A more recent study suggests that estrogen can prevent cholinergic-induced constriction of isolated mouse bronchial rings by activating the nitric oxide-cGMP-protein kinase G pathway to increase BK_{Ca} channel activity (17).

As discussed above, estrogens exert most of their effects through ER α or β, and both nuclear receptors are expressed in the lung. We recently found that naive αERKO mice exhibit substantially enhanced airway responsiveness to inhaled methacholine compared to wild type mice (8). Expression of the M2 muscarinic receptor was markedly reduced in αERKO female mice relative to wild type controls, and tracheas from αERKO female mice released more acetylcholine in response to electrical field stimulation than tracheas from wild type controls (8). M2 muscarinic receptors were also dysfunctional in these mice as evidenced by a lack of effect
of gallamine, a selective M2 muscarinic receptor antagonist, on the contractile response of αERKO tracheas to electrical field stimulation. Downregulation of M2 muscarinic receptor expression and function leads to increased acetylcholine in the neuromuscular junction and results in enhanced bronchoconstriction following cholinergic agonist stimulation. Alteration in expression and function of these receptors has been implicated in the pathogenesis of AHR. The findings of AHR in the αERKO mice point to modulation of a critical AHR mechanism by ER signaling. Interestingly, lack of ERα did not alter the inflammatory response in the allergic airway despite having profound effects on the development of allergen-induced AHR (8).

**Acute lung injury models**

In contrast to their effects in allergic airway disease, androgens appear to be detrimental in the pathogenesis of LPS-induced airway inflammation and hyperresponsiveness (6). Our laboratory recently demonstrated that following LPS aspiration, male mice develop significantly greater AHR and airway inflammation than female mice (6). Gonadectomy decreased airway inflammation in males but not females, whereas administration of exogenous testosterone to intact females increased their inflammatory responses to levels observed in intact males. LPS-induced AHR was also decreased in castrated males and increased in females receiving exogenous testosterone (6).

Speyer and colleagues investigated the effects of estrogen on LPS induced acute lung inflammation (69). All injury endpoints were substantially greater in male and ovariectomized females compared to intact females, and estrogen replacement in ovariectomized mice restored many of the endpoint values to levels found in intact females (69). Their data specifically suggested that estrogen suppresses lung inflammatory responses through effects on vascular cell
adhesion molecules and proinflammatory cytokines (69). Similarly, in the rat, estrogen attenuated tissue damage associated with carrageenan-induced pleurisy and the effects were blocked by coadministration of the estrogen receptor antagonists ICI 182,780 or tamoxifen, suggesting a receptor mediated effect (13). As apoptosis is important in the resolution of inflammation, Tesfaigzi and co-workers tested the hypothesis that reduced levels of Bcl-2, an important regulator of apoptosis, may play a role in sex-specific differences in response to LPS (76). Interestingly, the faster recovery of female than male mice from LPS-induced sickness, was abrogated when Bcl-2 levels were reduced (76).

Several animal studies have investigated a sex disparity in the resistance and susceptibility to shock induced lung injury. Hemorrhagic shock leads to a series of early physiologic events including the shunting of blood from the splanchnic to central circulation resulting in gut injury and it is thought that shock induced lung injury is secondary to gut injury (10, 16). Male sex hormones potentiate whereas female hormones ameliorate shock induced gut and lung injury (1, 10). Estrous or proestrous rats were more resistant to shock induced gut and lung injury and it is thought that their resistance to gut injury underpins their resistance to lung injury (10). Castration of male rats decreased susceptibility to both lung and gut injury (1). Recently Yu and colleagues showed that the protective effects of estrogen on lung injury after trauma-hemorrhage were mediated via ERβ and possibly through ERβ induced downregulation of iNOS (88). Data from Toth and colleagues suggested that decreased neutrophil priming and activation in proestrus females, compared to males, resulting in decreased cellular injury and organ damage, may be one mechanism leading to improved outcome in females (80).

**Respiratory infection**
Sex differences in immune function are well established in humans and animals (63). Males typically exhibit weaker humoral and cell mediated immune responses compared to females (83). While there are several examples of the effects of sex and sex hormones on pulmonary infection in humans, there are much fewer examples of animal models of respiratory infection where sex has been shown to influence susceptibility and severity of disease. In the case of *Pseudomonas aeruginosa*, female mice were more susceptible to lung infection than males (22). Females displayed greater weight loss, higher bacterial load and mounted a more rigorous inflammatory response in the lungs than males (22). In contrast, male mice developed more severe granulomatous lung lesions than females following infection with *Mycobacterium marinum* or *Mycobacteria intracellulare*, and testosterone exacerbated disease severity in females (85, 86). Murine respiratory mycoplasmosis (MRM) caused by *Mycoplasma pulmonis* infection has many similarities to human mycoplasma respiratory disease. In MRM, male mice developed more severe alveolar pneumonia than female mice (87). Interestingly, gonadectomy of mice of either sex reduced the severity of mycoplasma lung disease and the numbers of mycoplasma organisms recovered from lungs (87). Male rats were more susceptible than female rats to *Strongyloides venezuelensis* lung infection (60). Castration of male animals significantly increased host resistance whereas ovariectomy of female animals significantly decreased host resistance (60). Susceptibility significantly increased in ovariectomized females given testosterone or decreased in ovariectomized females given estrogen suggesting that both male and female hormones are important in host resistance to this parasite (60).

**Lung toxicology studies**
Animal models are widely used in pulmonary toxicology to examine issues such as host susceptibility (33) and to understanding the mechanisms, and pathology associated with environmental exposures (77). However, few published studies have examined in detail the role of sex and sex hormones in these models. The lungs of female mice are more susceptible and respond differently to naphthalene, a prominent component of sidestream cigarette smoke (82). Van Winkle and co-workers found that in female mice, injury occurs earlier and that the affected cells are farther up the airway tree than in males who received the same naphthalene dose (82).

It has been suggested that the increased susceptibility in females may be related to differences in naphthalene metabolism, distribution of susceptible cells and/or a different intracellular mechanism of toxicity (82). The estrous cycle can alter naphthalene metabolism in female mouse airways (70). Polycyclic aromatic hydrocarbons (PAH), such as benzo[a]pyrene (BaP), are widespread environmental pollutants and are thought to be an etiological factor in human cancers. Female CD1 and A/J mice are more susceptible to developing BaP induced lung tumors than their male counterparts, an effect that may be related to differential expression of glutathione S-transferases, enzymes which play a major role in BaP detoxification (66, 68).

Banka and co-workers recently showed that the estrogen status of the host can have a major impact on tumor cell survival, arrest and/or invasion in the lung (2).

**Summary**

Sex and sex hormones play a major role in the lung under both physiological and pathophysiological conditions in animals. These sex differences and the influences of sex hormones on the lung are summarized in Table 1. This review highlights the importance of sex -
specific research and the importance of considering sex and hormonal status as modifying factors when studying lung physiology and disease.
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Figure 1

Overview of the sex steroid hormone biosynthetic pathway and associated nuclear receptors; P450scc, P450-linked side chain cleaving enzyme; CYP17, cytochrome P45017; 3βHSD, 3β-hydroxysteroid dehydrogenase; 17βHSD, 17β-hydroxysteroid dehydrogenase; PR, progesterone receptor; AR, androgen receptor; ER, estrogen receptor.
<table>
<thead>
<tr>
<th>Sex Difference</th>
<th>Hormone Effect</th>
<th>Receptor Involvement</th>
<th>Effect of Gonadectomy</th>
<th>Proposed Mechanisms/ Pathways</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFTR, ENaC</td>
<td>F &gt; M</td>
<td>(E +P)</td>
<td></td>
<td></td>
<td>(74)</td>
</tr>
<tr>
<td>Sa</td>
<td>F &gt; M</td>
<td>↑E</td>
<td>ERα</td>
<td>↓O</td>
<td>(41, 42)</td>
</tr>
<tr>
<td>Alveolar size</td>
<td>F &lt; M</td>
<td>NE(A)↓E</td>
<td>ERα</td>
<td>↑O</td>
<td>(41, 42)</td>
</tr>
<tr>
<td>Lung elastic tissue recoil</td>
<td></td>
<td></td>
<td>ERβ</td>
<td></td>
<td>(39, 40)</td>
</tr>
<tr>
<td>TLC</td>
<td>F &lt; M</td>
<td></td>
<td></td>
<td></td>
<td>(59)</td>
</tr>
<tr>
<td>Airway size</td>
<td>F &gt; M</td>
<td></td>
<td></td>
<td></td>
<td>(59)</td>
</tr>
<tr>
<td>Hypoxia response/survival</td>
<td>F &gt; M</td>
<td>(E +P)</td>
<td></td>
<td></td>
<td>(44, 48, 71, 75)</td>
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<tr>
<td>TV, MV, PIF, PEF</td>
<td>F &lt; M</td>
<td></td>
<td>ERα</td>
<td></td>
<td>(8)</td>
</tr>
<tr>
<td>Frequency</td>
<td>F = M</td>
<td></td>
<td>ERα, ERβ</td>
<td></td>
<td>(8)</td>
</tr>
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<td>F &gt; M</td>
<td></td>
<td></td>
<td></td>
<td>(37)</td>
</tr>
<tr>
<td>Bleomycin induced Fibrosis (rats)</td>
<td>F &gt; M</td>
<td>↑E</td>
<td></td>
<td>↓O</td>
<td>(19)</td>
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<tr>
<td>Bleomycin induced Fibrosis (mice)</td>
<td>F &lt; M</td>
<td></td>
<td></td>
<td></td>
<td>(23)</td>
</tr>
<tr>
<td>Allergic airway disease</td>
<td>F &gt; M</td>
<td>↑E, ↑P</td>
<td>↑C, ↓O</td>
<td>Regulatory T-cells</td>
<td>(11, 24, 25, 35, 45, 64)</td>
</tr>
<tr>
<td>Airway Hyperresponsiveness</td>
<td>F &lt; M</td>
<td>↑A ↓E</td>
<td>ERα</td>
<td></td>
<td>(6-8, 15, 17)</td>
</tr>
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<td>F &lt; M</td>
<td>↑A ↓E</td>
<td>↓C</td>
<td>Adhesion molecules, apoptosis</td>
<td>(6, 69, 76)</td>
</tr>
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<td>ERβ</td>
<td>↓C</td>
<td>iNOS, neutrophil priming</td>
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<td>F &lt; M</td>
<td>↑A</td>
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<td>F &lt; M</td>
<td>↓O ↓C</td>
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<td>F &lt; M</td>
<td>↑A ↓E</td>
<td>↓C ↑O</td>
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<td>(60)</td>
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<td></td>
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<td>metabolism</td>
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A, androgen; AChE, acetylcholinesterase; AR, androgen receptor; BKCa, calcium-activated potassium channel; CFTR, cystic fibrosis transmembrane conductance regulator; C, castration; E, estrogen; ER, estrogen receptor; ENaC, epithelial sodium channel; F, female; GM-CSF, granulocyte macrophage colony stimulating factor; 3 -
HSD, 3α-hydroxysteroid dehydrogenase; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; M, male; MRM, murine respiratory mycoplasmosis; MV, minute ventilation; NE, no effect; O, ovarietomy; P, progesterone; PAH, polycyclic aromatic hydrocarbons; PDGF, platelet derived growth factor; PEF, peak expiratory flow; PIF, peak inspiratory flow; Sa, surface area (alveolar); TGF-β R, transforming growth factor-beta receptor; TLC, total lung capacity; TV, tidal volume.