

All Men Are Created Equal?

New Leads in Explaining Sex Differences in Adult Asthma

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The incidence of asthma has a strong sex bias. Asthma not only occurs more frequently among adult women in the reproductive years of their lives, but adult females also exhibit a more severe form of asthma. However, we are still far from explaining why these differences occur and using them to our advantage when treating patients. Women are still underrepresented in most clinical trials investigating new drugs, yet knowledge of their responses to drugs in asthma is essential in developing optimal treatments for both men and women. Sex hormones undoubtedly play a major role in the differences between male and female asthma, but little is known about how sex hormones affect the pathogenesis of asthma and what their targets are. It therefore seems prudent to first uncover in what ways asthma differs in men and women before embarking on trying to elucidate how sex hormones affect these processes. Understanding the mechanisms involved will eventually also improve treatment options for both men and women.

Keywords: innate immunity; sex differences; sex hormones; macrophages; allergy

The influence of sex on disease mechanisms and therapy has attracted more attention in the past decades. However, we are still a long way away from explaining why these differences occur and using them to our advantage when treating patients. Women are still underrepresented in most clinical trials investigating new drugs (1), and therefore female health care is compromised by a lack of sex-specific information about these drugs (2). This pertains to asthma as well: mechanisms explaining sex differences in asthma pathophysiology remain largely unexplored and little attention is paid to differences in treatment responses between men and women. Yet studies investigating these aspects of sex differences in asthma are essential in developing optimal treatments for both men and women. We here report on new leads in explaining sex differences in asthma.

SEX DIFFERENCES IN ASTHMA

The incidence of asthma has a strong sex bias (3–5). Asthma not only occurs more frequently among adult women in the reproductive years of their lives, but females also exhibit a more severe form of asthma (6–8). Visits to the emergency department, subsequent hospitalizations, as well as admissions to the intensive care unit for acute severe asthma are more common among female than male adults with asthma (9–24). Some studies have also shown that women with asthma have more problems in reaching asthma control (25, 26) and experience longer hospital stays per admission and longer intubation times for respiratory failure (11, 13, 27, 28); yet others showed no

differences (19) or longer intensive care stays for men with asthma (17). In addition, asthma in adult women is associated with an excess mortality risk (21, 29–43).

EFFECTS OF SEX HORMONES ON ASTHMA

There is substantial support for a role of female sex hormones in the development of asthma, starting with the fact that the prevalence of asthma and other atopic conditions is higher in boys than girls before puberty and reverses to a higher prevalence in girls and women after puberty, when sex hormone levels have increased (44). This phenomenon is not caused solely by increased loss of established asthma in boys, but also appears to be due to a late incidence of asthma among girls (45).

The female sex hormones have been linked to promoting the development of asthma because an earlier menarche increases the risk of developing asthma in females (46, 47). Early-onset menarche is associated with higher estrogen concentrations and greater cumulative estrogen and progesterone concentrations than is late-onset menarche (48). Furthermore, 30 to 40% of menstruating females with asthma experience perimenstrual asthma worsening, with increased symptoms and a greater likelihood of hospitalization (49, 50). This increase could theoretically be due to increases or decreases in hormone levels (51, 52) or to a change in hormone ratio (53). However, there is also an unknown and possibly variable time lag between these hormonal changes and the worsening of asthma, which makes it difficult to pinpoint which levels of hormones or which changes in those levels affect the severity of the disease. Tan and colleagues described an interesting mechanism to account for increased premenstrual symptoms when progesterone levels are high (54). Their studies showed that an increase in progesterone during the luteal phase of the cycle corresponded with an increase in β_2 -adrenoreceptors and a maximal response to isoprenaline. In females with asthma, however, the up-regulation of β_2 -adrenoreceptor density and function by progesterone was lost and turned into a down-regulation of receptor density and function.

Effects of oral contraceptives on the development of asthma or the manifestation of symptoms have not contributed to the elucidation of how sex hormones affect asthma. Results of studies showed a decreased risk of developing asthma with increased length of oral contraceptive use (55), no effect (56), and an increased risk of asthma with oral contraceptive use (46, 57).

Additional proof indicating a role of sex hormones in asthma development is the fact that asthma incidence declines in women after menopause as compared with men and younger women, but not in women who receive hormone replacement therapy to treat symptoms of menopause (56, 58–61).

The previously mentioned studies, taken together, have given us convincing evidence that asthma is affected by sex hormones. Unfortunately, none of these studies, with the exception of the study by Tan and colleagues (54), has yielded information about how sex hormones modulate asthma development and symptoms and which cellular mechanisms are being affected. These mechanistic studies are difficult to set up in humans and therefore animal models of asthma could help us to generate new hypotheses.

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DATA FROM ANIMAL MODELS

A small number of investigations in animal models have tried to elucidate how female sex hormones affect asthma. The few studies published have focused less on mechanisms and rather more on inflammatory and allergic end points such as airway hyperresponsiveness, IgE levels, and eosinophils. Yet these studies failed to provide conclusive proof of the effects of female sex hormones on asthma development because they reported both inhibition and aggravation of airway inflammation by estrogen and progesterone (62–66). In addition, in an interesting study by Okuyama and colleagues it was shown that sex differences in airway inflammation are caused not only by the hormonal environment during inflammation, but also by intrinsic differences between male and female immune cells (67). However, what those differences are was not further investigated.

Part of the controversy over the effects of female sex hormones may be explained by differences in the expression of their receptors. Both estrogen and progesterone receptors are expressed on resident lung cells and invading immune cells (68–70), but none of the studies mentioned previously looked into expression patterns of estrogen and progesterone receptors. For instance, we found significant up-regulation of the estrogen receptor- β (ER β) in lung tissue in our mouse model of asthma in both males and females (Figure 1), which could dramatically alter the effect of circulating estrogens on resident lung cells. It has been suggested that ER β may have anti-inflammatory properties (69, 71), which could explain the up-regulation of this receptor in our animal model of asthma as a negative feedback mechanism. Catley and colleagues used this hypothesis to test the effectiveness of an ER β agonist in a rat model of asthma, but found no effects on airway inflammation (71). However, as a critical note, this may also be because up-regulation of ER β in lung tissue did not occur after asthma induction in their model.

Interestingly, a longitudinal decline in lung function in patients with asthma occurred specifically in females in association with estrogen receptor polymorphisms, as did the development of airway hyperresponsiveness (72). This suggests that not only levels of hormones, but also sex-specific changes in their receptors, may affect asthma development and progression.

Results from these animal models show that the influence of sex hormones is most likely a complex interplay of estrogens, progesterone, and their receptors in the various mechanisms involved in the pathogenesis of asthma, including the maturation of immune cells. To be able to tease out their effects, it would help if we knew which disease processes are different between males and females to identify the most likely targets for the modulation by sex hormones.

INVESTIGATING SEX-SPECIFIC ASTHMA PATHOGENESIS

We and others have shown in mouse models of asthma that female mice are also more susceptible to the development of airway inflammation than are male mice (73–75). We have used this model to elucidate which processes leading up to asthma are different between males and females. Our study indicated that the differences between males and females may lie in the adaptive immune response, for example, differences in regulatory T-cell function (73). In follow-up work we tried to pinpoint which part of the immunological cascade leading up to asthma is different between males and females. We could not prove that there are functional or numerical differences in regulatory T cells between males and females (76). We did, however, find significant differences in macrophages, cells of the innate

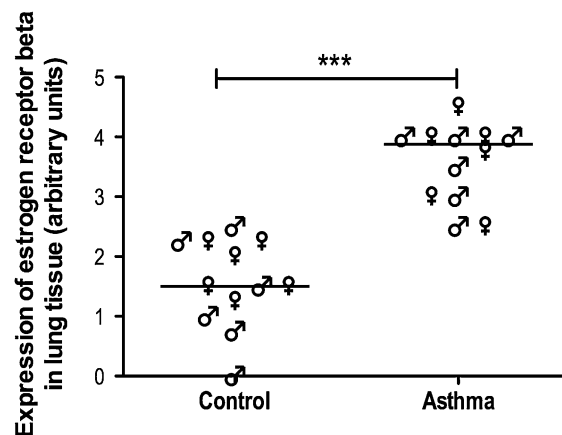


Figure 1. Development of ovalbumin-induced allergic airway inflammation significantly up-regulates estrogen receptor- β (ER β) expression on cells within lung tissue in both male and female mice. *** $P < 0.001$ in Mann-Whitney test.

immune response. The innate immune system is emerging as an important component of asthma pathogenesis (77). Until recently, it was regarded simply as the first-line defense against microbes and allergens, but it has become increasingly clear that macrophages and other cells of the innate immune system actively orchestrate adaptive immune responses (77–79). Macrophages are among the most abundant cells of the innate immune system present in lungs and have a crucial role in maintaining tissue homeostasis. They have a flexible phenotype that not only allows them to respond quickly to pathogens entering the lung, but also to suppress inflammatory responses and induce tissue repair (80, 81). In addition, the alternatively activated phenotype that is responsible for tissue repair has been implicated in asthma development. Exciting new data show that markers of alternative activation are associated with the induction and clinical expression of asthma (82–86). We have demonstrated that alternatively activated macrophages amplify allergy airway inflammation in mice, and also that female mice have more of these macrophages than do males. This suggests that macrophages may play an active role in female asthma and possibly constitute an interesting new target for therapy. Studying how female sex hormones subsequently affect macrophage responses in the lung is an interesting novel approach in trying to explain sex differences in asthma.

The possibly important role of innate immune responses in female asthma is interestingly accompanied by a differential response to treatment in asthma. Women with asthma were found to benefit less from corticosteroid therapy compared with men with asthma in a retrospective longitudinal study (87). The innate immune response is intrinsically unresponsive to corticosteroids, as was elegantly shown by Zhang and colleagues (88). Therefore, if innate immune responses play a more important role in female asthma, it would explain why corticosteroids work less well in women. It would also explain why women are more prone to severe asthma, which is characterized by decreased steroid sensitivity (77).

SUMMARY

Sex hormones undoubtedly play a role in the differences between male and female asthma. Yet how and what they affect is for now a mystery. It therefore seems prudent to first uncover in what way male and female asthma differ before embarking on trying to elucidate how sex hormones affect these processes. Understanding the mechanisms involved will

eventually also improve treatment options for both men and women.

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