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Sex steroid signaling: Implications for lung diseases

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ABSTRACT

There is increasing recognition that sex hormones (estrogen, progesterone, and testosterone) have biological and pathophysiological actions in peripheral, non-reproductive organs, including the lung. Clinically, sex differences in the incidence, morbidity and mortality of lung diseases such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, lung cancer and pulmonary hypertension have been noted, although intrinsic sex differences vs. the roles of sex steroids are still not well-understood. Accordingly, it becomes important to ask the following questions: 1) Which sex steroids are involved? 2) How do they affect different components of the lung under normal circumstances? 3) How does sex steroid signaling change in or contribute to lung disease, and in this regard, are sex steroids detrimental or beneficial? As our understanding of sex steroid signaling in the lung improves, it is important to consider whether such information can be used to develop new therapeutic strategies to target lung diseases, perhaps in both sexes or in a sex-specific manner. In this review, we focus on the basics of sex steroid signaling, and the current state of knowledge regarding how they influence structure and function of specific lung components across the life span and in the context of some important lung diseases. We then summarize the potential for sex steroids as useful biomarkers and therapeutic targets in these lung diseases as a basis for future translational research in the area of gender and individualized medicine.

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1. Introduction

There are inherent sex differences in the human lung which are apparent from early in life (indeed in utero) and manifest in different forms throughout the lifespan. Here, changes in lung structure and function at key life stages such as puberty, pregnancy, menopause and in aging suggest a modulatory role of sex steroids. This is particularly relevant, given the considerable epidemiological evidence for a role for sex in the incidence, susceptibility and severity of a number of lung diseases that create a healthcare and financial burden of ~35 million individuals and 400,000 deaths in the US (ALA, 2008). For example,

Abbreviations: 3β-HSD, 3β-hydroxysteroid dehydrogenase; AR, androgen receptor; ERE, estrogen response elements; ASM, airway smooth muscle; cAMP, cyclic adenosine monophosphate; COPD, chronic obstructive pulmonary disease; CPA, cyclopiazonic acid; CSE, cigarette smoke extract; CYP, cytochrome P450s; DBD, DNA binding regions; DCs, dendritic cells; DHEA, dehydroepiandrosterone; DHT, 5α-dihydrotestosterone; E_2, 17-β-estradiol; ECM, extracellular matrix; ER, estrogen receptor; HRT, hormone replacement therapy; IPF, idiopathic pulmonary fibrosis; LBD, ligand-binding domain; NANC, non-adrenergic non-cholinergic; NO, nitric oxide; NOS, nitric oxide synthase; PF, pulmonary fibrosis; PR, progesterone receptor; SHS, second hand smoke; SOCE, store operated Ca^{2+} entry

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asthma is more common in pre-pubescent males, but becomes more common in females after puberty (Becklake & Kauffmann, 1999; Bjornson & Mitchell, 2000; Caracta, 2003; Carey et al., 2007a; Melgert et al., 2007; Jensen-Jarolim & Untersmayr, 2008) such that the incidence, frequency and severity of asthma are greater among adult women, compared to men (Bjornson & Mitchell, 2000; Caracta, 2003; Carey et al., 2007a; Melgert et al., 2007; Jensen-Jarolim & Untersmayr, 2008). Similarly, differences between men and women in the incidence/frequency of and morbidity/mortality associated with smoking-induced lung disease have also been noted, not all of which can be explained by differences in smoking rates between the sexes (Troisi et al., 1995; Mannino et al., 2002; Hughes & Jacobson, 2003; Hughes et al., 2008). What is less clear from epidemiological data such as these are the relative contributions of intrinsic sex differences in lung structure and/or function vs. sex steroids: a topic of considerable interest and ongoing research.

The contrasts between men and women in a range of diseases have led the Institute of Medicine to emphasize that sex is or should be a biological variable for research as well as clinical practice norms ("Exploring Biological Contributions to Human Health—Does Sex Matter?"; http://www.nap.edu/openbook.php?isbn=0309072816). Although this report really targets sex differences per se in non-reproductive organ systems, the respiratory system (upper and lower conducting airways, lung parenchyma) and lung diseases were surprisingly not highlighted. More recently, the NIH has announced the requirement that grant applicants report the sex of animals and cells in pre-clinical studies. However, this emphasis is also on intrinsic sex differences rather than any modulating role sex steroids may play in human lung health and disease. Nonetheless, perspectives, editorials and reviews in several journals all highlight the idea that sex steroids "do more" than play a role in reproductive function. Certainly, this has been most established in the cardiovascular (Arain et al., 2009; Konhilas, 2010; Leuzzi et al., 2010; Miller, 2010; Perez-Lopez et al., 2010), metabolism (Beierle et al., 1999; Bigos et al., 2009; Greenhill, 2011; Wang et al., 2011), and cognition (McEwen & Alves, 1999; Manson, 2008; Gillies & McArthur, 2010; Hines, 2010; Janicki & Schupf, 2010; McEwen, 2010; Reddy, 2010) arenas, but there are now increasing reports of sex steroid effects in different lung components, and how they may play a role in important diseases such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, cancer and even pulmonary hypertension. Accordingly, the major goal of this review is to highlight this research relating to sex steroids and their effects on lung components in health and disease. Given that most of the research to date is on the adult lung, which also represents the majority of healthcare burden of lung disease, we will focus on this aspect, with brief mention of how influence of sex steroids early in life may have bearing for adult lung health and disease. Finally, we will introduce the concept of sex steroids and their signaling which could form a platform for diagnosis and therapy in lung diseases in the context of individualized medicine. Regarding intrinsic sex differences and the lung, the reader is referred to some recent reviews on this topic (Tam et al., 2011; Gonzalez-Arenas & Agramonte-Hevia, 2012; Townsend et al., 2012a; Martin & Pabelick, 2014; Prakash et al., 2014).

2. Brief review of sex steroid biology

In order to understand sex steroid effects in the lung, it is important to appreciate how estrogens, progesterone, testosterone or even their biologically-active metabolites are produced and exert their action. Here, we emphasize that substantial cellular, tissue, or even species heterogeneity of sex steroid action can occur due to modulation of the basic sex steroid signaling pathways, as well as interactions between sex steroids (particularly in women where estrogens and progesterone are normally present concurrently).

In terms of sex steroid production, estrogen, progesterone and testosterone are all derived from cholesterol via well-established pathways (Payne & Hales, 2004; Ghayee & Auchus, 2007) (Fig. 1). Briefly, cholesterol is converted to pregnenolone by the P450 side chain cleavage enzyme located in the mitochondrial membrane. Pregnenolone can be converted to either progesterone (via 3β-hydroxysteroid dehydrogenase, 3β-HSD) or dehydroepiandrosterone (DHEA via cytochrome P450 17). DHEA may be further converted to androstenedione (3β-HSD) and subsequently testosterone (17β-HSD) or estrone (via aromatase). Estrone and testosterone may then be converted to estradiol (via 17β-HSD and aromatase, respectively).

Although sex steroids are mainly produced by the gonads, and contribute substantially to circulating levels of these hormones, there is considerable evidence for local production in peripheral tissues of non-reproductive organs such as the heart, multiple vascular beds, breast, brain, and even the lung (Labrie et al., 1991; Labrie, 2003; Luu-The & Labrie, 2010), with the pattern of steroid production being dependent on which enzymes of the cholesterol pathway are present within specific tissues. The relevance of these non-gonadal sources lies in the high possibility that local sex steroid production or its metabolism within specific tissues can lead to substantial differences between local steroid levels vs. that seen in the circulation. Accordingly, it is possible that some of the paradoxical effects of sex steroids between organ systems and diseases involve the effects of local steroid regulation and effects. A prime example of this is the so-called "estrogen paradox" of pulmonary hypertension in young women while estrogens are thought to be protective in the coronary circulation. Multiple experimental animal studies have found estrogen and its metabolites to be protective against pulmonary hypertension, with better outcome in female animals and exacerbation following ovariectomy, but epidemiological data in humans indicate greater incidence of pulmonary hypertension in female patients, with some clinical studies indirectly linking estrogen to increased risk of portopulmonary hypertension, and others showing increased estrogen metabolism and higher levels of estrogen metabolites to be enhancing pulmonary vascular remodeling (see Umar et al., 2012; Martin & Pabelick, 2014 for recent reviews).

Since both gonadally-derived and local sex steroids (Labrie et al., 1991; Labrie, 2003; Luu-The & Labrie, 2010) contribute to overall concentrations systemically and within tissues, it is important to consider concentrations of specific sex steroids that are typically noted. This is particularly important given life events such as puberty in men and women, pregnancy and menopause in women, and aging in both sexes. Here, it is not uncommon to see different formats (molar concentrations vs. serum levels) being used in studies, which makes comparisons sometimes difficult. We have previously compiled comparative data from different sources (Lippe et al., 1974; Cummings et al., 1998; Elmlinger et al., 2002) in this regard (Townsend et al., 2012a) to provide normal ranges of testosterone, estradiol, and progesterone in men vs. women in different life stages (non-pregnant, pregnant, and post-menopausal). Interestingly, the range of testosterone is usually stable in both males (2–15 ng/ml or 6–50 nM) and females (<1.5 ng/ml or 5 nM) throughout life. While men express pg/ml (pM) estradiol and ng/ml (nM) progesterone levels, the levels of these hormones obviously fluctuate substantially in women, ranging from 20 pg/ml estradiol and 0.3 ng/ml progesterone in follicular phase in non-pregnant and post-menopausal women to 40 ng/ml estradiol and 300 ng/ml progesterone in pregnant women. The importance of these level fluctuations lies in their relative contribution to the local level of any sex steroid. Thus, for example, tissue production of estrogens (e.g. via aromatase-mediated testosterone conversion) may become more prominent in post-menopausal women as well as in aging men, while separately, the influence of progesterone may wane in these populations. Conversely, the very circulating levels of estrogen and progesterone in women may be more important in pregnancy unless tissue metabolism of these steroids can modulate the local levels that impact cells within an organ. There is currently very little information on these issues relevant to the lung.