doi: 10.13241/j.cnki.pmb.2015.10.045

雌激素在肺组织中的作用机制概述 *

袭荣刚[1,2] 刘中洋[1,2] 屈 超[1,2] 杨 阳[1,2] 王晓波[1,2△]

（1 沈阳军区药物研究所 辽宁 大连 116015;2 解放军第 210 医院 辽宁 大连 116015）

摘要: 在妇女中,哮喘、慢性阻塞性肺病(COPD)、囊肿性纤维化(CF)等肺部疾病发病率不断增加。大量实验研究表明,女性肺部、气管疾病患者的病情随着女性生理周期存在波动,因此,在体内雌激素和孕激素含量变化可能与肺部疾病的病情轻重存在一定的关系。雌激素包括三类:雌三醇、雌二醇、雌酮,性激素主要与他们的特异性受体结合发挥作用:雌激素受体(ERα、ERβ),孕激素受体(PR-A、PRB),和雄激素受体(AR)。雄激素受体只有哺乳动物生殖腺中有表达;雌激素受体和孕激素受体不仅在哺乳动物雌性、雄性生殖腺中有表达,在乳腺、骨、心肌、肺和脑等组织器官中均有表达。临床实验数据已经表明,男女肺部疾病发病率存在明显差异,本文主要对雌激素与肺组织之间关系作一简要综述。

关键词: 肺部疾病;生理周期;雌激素

中图分类号: Q579.13;Q593 **文献标识码:** A **文章编号:** 1673-6273(2015)10-1971-02

The Role of Estrogen in Lung*

XI Rong-gang[1,2], LIU Zhong-yang[1,2], QU Chao[1,2], YANG Yang[1,2], WANG Xiao-bo[1,2△]

(1 Institute of Materia Medica of Shenyang Military Region, Dalian, Liaoning, 116015, China;

2 The 210th Hospital of PLA, Dalian, Liaoning, 116015, China)

ABSTRACT: The prevalence, morbidity, and mortality of inflammatory lung diseases such as ast- hma, chronic obstructive pulmonary diseas e (COPD) and cystic fibrosis (CF) are increasing in women. Some large epidemiologic studies suggest that lung function fluctuates during the menstrua l cycle in female patients with airways disease but not in women without disease, suggesting that circulating estradiol and progesterone may be involved in this process. There are three major naturally occurring estrogens in women:1) estriol, 2) estradiol, and 3) estrone; Sex steroid hormones act via their own unique receptors: estrogen receptor (ERα or ERβ), progesterone receptor (PR-A or PR-B), and an androgen receptor (AR). Androgen receptor is expressed primarily in mammalian reproductive tissues, ERα, ERβ, PR-A and PR-B expression have been noted not only in the mammalian female and male reproductive tracts, but also in the female mammary glands, bone, cardiovascular tissues, lung, and the brain. Taken together, clinical and invivo data have demonstrated a sex related difference that females may be more susceptible to the pathogene sis of lung diseases. In this paper , we review the relationship between estrogen and lung.

Key words: Lung disease; Physiological cycle; Estrogen

Chinese Library Classification(CLC): Q579.13; Q593 Document code: A

Article ID: 1673-6273(2015)10-1971-02

前言

哮喘、慢性阻塞性肺病(COPD)、囊肿性纤维化(CF)等肺部疾病存在性别差异。例如,在美国哮喘病人的 60%是妇女[1]。虽然 COPD 患病率男性多于女性,但是随着吸烟的女性不断增加，女性患 COPD 的比率不断增加,2000 年，在美国女性 COPD 致死率首次高于男性。调查 COPD 病人与吸烟关系时发现,女性患病与吸烟关系小于男性[2]。尽管 CF 是一种遗传病,但是,女性病人存活的时间远小于男性。总之,雌性肺部疾病的炎症反应明显高于雄性。因此,性激素与 COPD、CF 等肺部疾病的发病具有密切关系。因此本文主要对雌激素和孕激素对肺部疾病发病机理作一简要综述。

1 雌激素和孕激素

固醇类激素主要在性腺、前列腺中合成。胆固醇是所有固醇激素的前体。固醇首先在 P450 侧链裂开酶作用下转化为孕烯醇酮,继而生成雄激素和雌激素。雄激素在芳香化酶作用下转化为雌激素[3]。雌激素包括三类:雌三醇、雌二醇、雌酮。雌三醇主要在妊娠期发挥作用;雌二醇主要在雌性非妊娠期到绝经期前这段时间发挥作用;雌酮为雌性绝经期后起主要作用的雌激素。性激素主要与他们的特异性受体结合发挥作用:雌激素受体(ERα、ERβ),孕激素受体(PR-A、PRB),和雄激素受体

* 基金项目:国家“重大新药创制”科技重大专项(2009ZXJ09002-019)

作者简介:袭荣刚(1972-),男,教授,主任药师,主要研究方向:新药研发,电话:041139847087,E-mail: quchao__2006@163.com

△通讯作者:王晓波

(收稿日期:2014-08-26 接受日期:2014-09-20)

(AR)。雌激素较雌三醇和雌酮更容易与雌激素受体结合。性激素受体在肺组织中均有表达[4]。

2 雌激素和月经周期

雌激素、黄体酮、促黄体激素、促卵泡激素均有周期性变化。大多数情况下,女性月经周期为 28 天,分为卵泡期(1-13 天)和黄体期(14-28 天)两个时期。排卵期为月经周期的第 14 天。黄体期后期血清中含有低水平雌激素(≈ 0.15nM)和高水平孕酮(≈ 9.54-31.81);排卵期含有高水平雌激素(≈ 0.37-1.47)和低水平的孕酮 (≈ 0.95-9.54nM)。黄体期雌激素变化范围为 0.15-0.92nM,孕酮的变化范围为 9.54 -31.81nM[5]。但是,更年期血清中雌激素和孕酮水平都下降至月经周期的最低水平。

3 肺组织中雌激素通过 SHBG 与雌激素受体结合

性激素结合球蛋白(SHBG)是人类细胞质中重要的固醇结合蛋白。SHBG 首先在肝细胞中合成 SHBG 的糖基化形式[6]。在生物体中,SHBG 与雄激素和雌激素结合。正常的男性和女性体内睾丸素的 40-65%和雌激素的 20-40%与 SHBG 结合。SHBG 通过与性激素结合调节肺组织中性激素的浓度[7]。但是,一旦性激素从 SHBG 中游离出来,性激素将进入血浆中与细胞内的雌激素或者雄激素受体结合,调节细胞内基因表达[8]。因此,只有游离的性激素是生物激活剂[9]。由于睾丸素较雌激素优先与 SHBG 结合从而更多的雌激素处于游离状态,因此 SHBG 被看做雌激素功效的放大器。

4 雌激素受体和肺生理

众所周知,雌激素和孕酮受体在性发展过程中具有重要作用,但是目前它们超出生殖系统外的作用备受关注。雌激素受体包括 ERα 和 ERβ 两种类型 [10]; 孕激素受体包括 PR-A 和 PR-B 两种类型,且这 4 种性激素受体在大鼠、小鼠、人肺组织中均有表达[11]。雄激素受体只有哺乳动物生殖腺中有表达;雌激素受体和孕激素受体不仅在哺乳动物雌性、雄性生殖腺中有表达,在乳腺、骨、心肌、肺和脑等组织器官中均有表达[12]。肺组织中 ERβ 表达量较 ERα 高两倍。ERα 和 ERβ 属于核受体成员,配体与受体结合后激活启动子调节基因转录。雌激素受体包含一个 N- 端 DNA 结合域和 C- 端配体结合域[13]。在小鼠中敲除 ERα 或 ERβ 发现,两种雌激素受体对于雌鼠肺泡形成是必须的。ERα 参与肺泡分化, 保证肺在单位体积内肺泡数量。ERβ 调节细胞外物质的发生,保证肺正常弹性收缩。更重要的是,ERα 抵抗角叉菜引起的小鼠肺炎症反应, 但是,ERβ 却不起作用。ERα 抑制 NFκ B 表达从而抑制炎症相关基因表达[14]。

5 雌激素受体在肺组织中激活机制

雌激素调节细胞信号通路的确切机制目前仍没有完全清楚,主要因为性激素可以通过多条细胞信号转导通路调节基因转录和翻译[15]。自由激素假说认为,雌激素通过自由扩散的方式通过细胞膜进入细胞。雌激素与雌激素受体的配体结合域结合后引起受体构象发生改变,导致雌激素受体二聚化后进入细胞核[16]。雌激素受体 / 雌激素与 DNA 特意启动子序列(雌激素受体反应元件)结合,招募细胞核中其它因子从而促进雌激素受体反应元件下游基因转录 [17]。另一种假说认为, 雌激素与 SHBG 结合是代谢激活。现如今人们已经发现雌激素能与细胞膜上与 SHBG 结合的雌激素受体结合。雌激素与 SHBG 结合激活 cAMP 依赖的信号通路继而上调腺苷酸环化酶和其它下游信号分子[18]。这些现象已经通过分离肺上皮细胞得到验证。

6 小结与展望

雌激素不仅在人类及动物的生殖系统中发挥重要作用,而且参与消化系统、呼吸系统、神经系统等功能发挥。雌激素需与其受体(ERα、ERβ)结合发挥作用。研究发现,雌激素受体不同类型在肺中均有表达[19]。

哮喘、CF、COPD 等慢性疾病妇女发病率明显高于男性,但其具体机制目前尚不清楚。有研究表明,哮喘发生过程中,雌激素通过促进 TH2 反应、孕激素通过促进 TH1 反应而发挥作用重要作用[20]。CF 发生过程中,雌激素抑制 Cl^- 分泌,促进粘液的产生而发挥作用。香烟烟雾的体内消除需要两阶段酶起作用[21]。研究发现,雌激素显著上调第一阶段酶的活性导致有毒物质的沉积,促使 COPD 的发生[22]。随着女性肺部疾病发病率不断增加,了解雌激素在肺部炎症反应过程中的作用具有重要的意义。探讨雌激素在肺部生理作用及作用机制为慢性肺病的治疗提供新的理论依据。

参 考 文 献(References)

[1] Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States [J]. NCHS Data Brief, 2010, 2012(94):1-8

[2] Silverman EK, Weiss ST, Drazen JM, et al. Gender-related differences in severe, early-onset chronic obstructive pulmonary disease[J]. Am J Respir Crit Care Med, 2000, 162(6): 2152-2158

[3] Mendelsohn ME, Karas RH. Molecular and cellular basis of cardiovascular gender differences[J]. Science, 2005, 308(5728): 1583-1587

[4] Carey MA, Card JW, Voltz JW, et al. The impact of sex and sex hormones on lung physiology and disease: lessons from animal studies[J]. Am J Physiol Lung Cell MolPhysiol, 2007, 293(2): L272-278

[5] Bowers LW, Cavazos DA, Brenner AJ, et al. Obesity enhances nongenomic estrogen receptor crosstalk with the PI3K/Akt and MAPK pathways to promote in vitro measures of breastcancer progression[J]. Breast Cancer Res, 2013, 15(4): R59

[6] Ronde W, van der Schouw YT, Muller M, et al. Associations of sex-hormone-binding globulin (SHBG) with non-SHBG-bound levels of testosterone and estradiol in independentlyliving men [J]. J Clin Endocrinol Metab, 2005, 90(1): 157-162

[7] Raps M, Rosendaal F, Ballieux B, et al. Resistance to APC and SHBG levels during use of a four-phasic oral contraceptive containing dienogest and estradiol valerate: a randomizedcontrolled trial [J]. J Thromb Haemost, 2013, 11(5): 855-861

(下转第 1976 页)

effect on neuroblastoma cells in vitro and in vivo[J]. Clin Cancer Res, 2006, 12(22): 6772-6780

[19] Samani AA, Yakar S, LeRoith D, et al. The role of the IGF system in cancer growth and metastasis: overview and recent insights[J]. Endocr Rev, 2007, 28(1): 20-47

[20] Frasca F, Pandini G, Sciacca L, et al. The role of insulin receptors and IGF-I receptors in cancer and other diseases [J]. Arch Physiol Biochem, 2008, 114(1): 23-37

[21] Van Golen, C.M., et al. Insulin-like growth factor-I receptor expression regulates neuroblastoma metastasis to bone [J]. Cancer Res, 2006, 66(13): 6570-6578

[22] Geoerger B, Brasme JF, Daudigeos-Dubus E, et al. Anti-insulin-like growth factor 1 receptor antibody EM164 (murine AVE1642) exhibits anti-tumour activity alone and in combination with temozolomide against neuroblastoma[J]. Eur J Cancer, 2010, 46(18): 3251-3262

[23] Zha J, Lackner MR. Targeting the insulin-like growth factor receptor-1R pathway for cancer therapy[J]. Clin Cancer Res, 2010, 16 (9): 2512-2527

[24] Rosenzweig SA1, Atreya HS. Defining the pathway to insulin-like growth factor system targeting in cancer [J]. Biochem Pharmacol, 2010, 80(8): 1115-1124

[25] Hartog H, Wesseling J, Boezen HM, et al. The insulin-like growth factor 1 receptor in cancer: old focus, new future [J]. Eur J Cancer, 2007, 43(13): 1895-1904

[26] Gualberto A. Figitumumab (CP-751,871) for cancer therapy [J]. Expert Opin Biol Ther, 2010, 10(4): 575-585

[27] Wang Y, Hailey J, Williams D, et al Inhibition of insulin-like growth factor-I receptor (IGF-IR) signaling and tumor cell growth by a fully human neutralizing anti-IGF-IR antibody[J]. Mol Cancer Ther, 2005, 4(8): 1214-1221

[28] Belfiore A. The role of insulin receptor isoforms and hybrid insulin/IGF-I receptors in human cancer[J]. Curr Pharm Des, 2007, 13 (7): 671-686

[29] Hendrickson AW, Haluska P. Resistance pathways relevant to insulin-like growth factor-1 receptor-targeted therapy [J]. Curr Opin Investig Drugs, 2009, 10(10): 1032-1040

[30] Buck E, Gokhale PC, Koujak S, et al. Compensatory insulin receptor (IR) activation on inhibition of insulin-like growth factor-1 receptor (IGF-1R): rationale for cotargeting IGF-1R and IR in cancer [J]. Mol Cancer Ther, 2010, 9(10): 2652-2664

[31] Zhao Q, Feng Y, Zhu Z, et al. Human monoclonal antibody fragments binding to insulin-like growth factors I and II with picomolar affinity [J]. Mol Cancer Ther, 2011, 10(9): 1677-1685

(上接第 1972 页)

[8] Fortunati N, Catalano MG, Boccuzzi G, et al. Sex Hormone- Binding Globulin(SHBG), estradiol and breast cancer[J]. Mol Cell Endocrinol, 2010, 316(1): 86-92

[9] Napoli N, Varadharajan A, Rini GB, et al. Effects of polymorphisms of the sex hormone-binding globulin (SHBG) gene on free estradiol and bone mineral density[J]. Bone, 2009, 45(6): 1169-1174

[10] Breithaupt-Faloppa AC, Fantozzi ET, Assis-Ramos MM, et al. Protective Effect of Estradiol on Acute Lung Inflammation Induced by an Intestinal Ischemic Insult is Dependent on Nitric Oxide [J]. Shock, 2013, 40(3): 203-209

[11] Drzewiecka H, Jagodzinski PP. Conversion of estrone to 17-beta-estradiol in human non-small-cell lung cancer cells in vitro [J]. Biomed Pharmacother, 2012, 66(7): 530-534

[12] Hamidi SA, Dickman KG, Berisha H, et al. 17beta-estradiol protects the lung against acute injury: possible mediation by vasoactive intestinal polypeptide[J]. Endocrinology, 2011, 152(12): 4729-4737

[13] Trotter A, Kipp M, Schrader RM, et al. Combined application of 17beta-estradiol and progesterone enhance vascular endothelial growth factor and surfactant protein expression in cultured embryonic lung cells of mice[J]. Int J Pediatr, 2009, 2009: 170491

[14] Guerrero-Vargas NN, Jurado R, Virto-Aguilar J, et al. Effects of 17beta-estradiol on the cytotoxicity of etoposide in a lung carcinoma cell line and its bioavailability in ovariectomized Sprague-Dawley rats[J]. Chemotherapy, 2010, 56(1): 32-38

[15] Mendel CM. The free hormone hypothesis. Distinction from the free hormone transport hypothesis[J]. J Androl, 1992, 13(2): 107-116

[16] Koehler KF, Helguero LA, Haldosen LA, et al. Reflections on the discovery and significance of estrogen receptor beta [J]. Endocr Rev, 2005, 26(3): 465-478

[17] Ivanova MM, Mazhawidza W, Dougherty SM, et al. Activity and intracellular location of estrogen receptors alpha and beta in human bronchial epithelial cells [J]. Mol Cell Endocrinol, 2009, 305(1-2): 12-21

[18] Massaro D, Massaro GD. Estrogen regulates pulmonary alveolar formation, loss, and regeneration in mice [J]. Am J Physiol Lung Cell Mol Physiol, 2004, 287(6): L1154-1159

[19] Brueckl WM, Al-Batran SE, Ficker JH, et al. Prognostic and predictive value of estrogen receptor 1 expression in completely resected non-small cell lung cancer [J]. Int J Cancer, 2013, 133(8): 1825-1831

[20] Shah SP, Gohil PV, Shah GB. Role of estrogen receptor- alpha in an experimental model of bronchial asthma [J]. Iran Biomed J, 2010, 14 (1-2): 41-48

[21] Wang Y, Cela E, Gagnon S, et al. Estrogen aggravates inflammation in Pseudomonas aeruginosa pneumonia in cystic fibrosis mice [J]. Respir Res, 2010, 11: 166

[22] Pedone C, Scarlata S, Napoli N, et al. Relationship Between Bone Cross-Sectional Area and Indices of Peripheral Artery Disease [J]. Calcif Tissue Int, 2013, 13(12): 7-9