



News Release

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ATS Press Room: 504-670-6926 (May 15 to 20)

Press conference time: May 16, 4:30 p.m. in the ATS Press Room (E-1)

Poster session time: 1:30-4:00 p.m. May 18

Location: CC-Room 291-292 (Second Level), Morial Convention Center

Estrogen May Reduce Airway Constriction in Women Patients With Asthma

ATS 2010, NEW ORLEANS— Female sex hormones may work with beta-agonists in reducing airway constriction, according to new bench research from the Mayo Clinic.

The findings will be presented at the ATS 2010 International Conference in New Orleans.

After puberty, women tend to have worse asthma symptoms and exacerbations than men. Women also experience changes in airway reactivity throughout their menstrual cycle, with pregnancy, and at the onset of menopause.

“Given these clinical observations, it is of interest to determine whether sex steroids (estrogen, progesterone) play a role in modulating airway tone,” said lead student researcher, Elizabeth A. Townsend, of the Mayo Clinic Department of Physiology and Biomedical Engineering, where she is completing her Ph.D. “What is less clear is whether sex steroids, especially estrogens, are detrimental or beneficial to airway function.”

“Increased bronchoconstriction, as in asthma, is directly influenced by the amount of intracellular calcium in airway smooth muscle. Therefore, we set out to explore the effect

of estrogens on calcium regulation in airway smooth muscle. Calcium regulation is a key factor in determining bronchoconstriction” said Ms. Townsend. “Since asthma symptoms have been documented to be worst when estrogen levels are lowest in the late luteal phase, we hypothesized that estrogens facilitate bronchodilation, rather than constriction.”

To test this hypothesis, Ms. Townsend and colleagues exposed human airway smooth muscle tissue and cells isolated from surgical lung samples to small doses of estradiol comparable to physiologic levels found in women. They found that acute (15 minute) exposure to estradiol at concentrations comparable to those experienced during a woman’s menstrual cycle decreased intracellular calcium in airway smooth muscle cells. Furthermore, small amounts of estradiol significantly decreased force production by human airways that had been stimulated with bronchoconstrictors, indicating increased bronchodilation.

Townsend and colleagues then asked whether estrogens could produce bronchodilation, and might the combination of commonly used bronchodilators (β_2 agonists) and estrogens be used to produce even greater bronchodilation? In laboratory studies using human airway smooth muscle cells, they found that combined treatment with estradiol and the β -agonist, isoproterenol (which non-selectively activates both β_1 and β_2 adrenergic receptors), had a synergistic effect on decreasing intracellular calcium and force more than either estradiol or isoproterenol alone. They also found that these effects may involve a common signaling pathway.

“These novel data suggest that estradiol has bronchodilatory properties, and may potentiate β_2 -agonist effects,” said Ms. Townsend. “The finding that estrogens interact synergistically with β -adrenoceptor signaling (perhaps using common pathways) to facilitate bronchodilation was exciting, and lends itself to further studies on interactions between sex steroids and β_2 -agonists”. But she and her team also cautioned that there is still considerable research necessary to fully understand the association between sex steroids and factors that contribute to asthma, before the information can be used clinically in patients to relieve asthma symptoms.

“Our work has only focused on the acute exposure of estrogens and the observed dilatory effects,” said Ms. Townsend. “In other organ systems and disease states, estrogens can have complex effects on inflammation, cell signaling and other factors also important in asthma and airway inflammation. Given our findings, we can ask a number of questions to guide future research: what is the effect of chronic exposure to estrogens on airway smooth muscle tone? Are there interactions between estrogen and progesterone in the airway? Are men and women different in their response to sex steroids in terms of airway tone? Can an inhaled combination of β_2 -agonist and estrogen be more effective at controlling asthma exacerbations, and potentially have a β_2 -agonist sparing effect?”

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“Mechanisms of Estrogen-Induced Bronchodilation in Human Airway Smooth Muscle”
(Session C108, Tuesday, May 18, 1:30-4:00 p.m., CC-Room 291-292 (Second Level),
Morial Convention Center; Abstract 2234)

**Please note that numbers in this release may differ slightly from those in the abstract.
Many of these investigations are ongoing; the release represents the most up-to-date data
available at press time.*

Mechanisms of Estrogen-Induced Bronchodilation in Human Airway Smooth Muscle

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Rationale: Clinically-observed differences in airway reactivity or asthma exacerbations in women following puberty, pregnancy, or altered hormonal status (menopause) all suggest a role of sex steroids in modulating airway function. Whether sex steroids (especially estrogen) are beneficial or detrimental to airway function is not clear. In the vasculature, estrogens are known to be vasodilatory. We have previously shown that acute exogenous estrogen decreases intracellular Ca^{2+} ($[\text{Ca}^{2+}]_i$) in airway smooth muscle (ASM), thereby facilitating bronchodilation. In other tissues, estrogens modulate cyclic nucleotide pathways and inhibit Ca^{2+} influx. In this study, we hypothesized that estrogens modulate cyclic nucleotide regulation, thus facilitating bronchodilation.

Methods and Results: In human ASM (isolated from surgical lung samples), we found that both estrogen receptors (ERs), ER α ; and ER β ; are expressed (Western analysis). Additionally, ER α ; and β_2 -adrenergic receptors (β_2 -AR) co-localize in the plasma membrane. In ASM cells loaded with the Ca^{2+} indicator fura-2, acute exposure to 17 β -estradiol (E_2 ; 100pM-10 nM) blunts $[\text{Ca}^{2+}]_i$ response to bronchoconstrictor agonists: effects prevented by ER (especially ER α) antagonists. Estrogen effects were largely attributable to decreased Ca^{2+} influx. In the presence of E_2 , the well-known inhibitory effect of the β_2 -AR agonist isoproterenol (100 nM) were potentiated. Force studies in bronchial rings (pre-contracted with 10 μM ACh) corroborated $[\text{Ca}^{2+}]_i$ results with E_2 (bronchodilation) as well as isoproterenol and E_2 (potentiated bronchodilation). Both β_2 -AR and E_2 individually increased cAMP production in ASM cells (competitive binding assay). Inhibition of protein kinase A activity (KT5720; 1 nM) attenuated E_2 effects on $[\text{Ca}^{2+}]_i$ in response to contractile agonist in fura-2 loaded ASM cells. Finally, plasma membrane translocation of the GTPase RhoA (involved in ASM Ca^{2+} sensitization during agonist exposure, and inhibited by PKA) was substantially reduced by acute E_2 pre-treatment.

Conclusion: These novel data suggest that in human ASM, clinically-relevant concentrations of estrogens act via ERs and the cAMP pathway to non-genomically produce bronchodilation. Activation of ERs may be a novel therapeutic mechanism in airway diseases such as asthma, especially in combination with established therapies such as β_2 -agonists which also act via cAMP.