# Estrogen may reduce airway constriction in women patients with asthma

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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 (Beta-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 beta-agonist, isoproterenol (which non-selectively activates both beta-1 and beta-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 beta-2-agonist effects," said Ms. Townsend. "The finding that estrogens interact synergistically with adrenoceptor signaling (perhaps using common pathways) to facilitate bronchodilation was exciting, and lends itself to further studies on interactions between sex steroids and beta-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 beta-2-agonist and estrogen be more effective at controlling asthma exacerbations, and potentially have a beta-2-agonist sparing effect?"

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