# Researchers move closer to identifying new class of asthma, COPD drugs

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Researchers in Baltimore have identified new compounds whichrelax airway muscles and may provide relief from shortness of breath for patients with COPD and asthma. The bitter-tasting compounds are at least as, if not more, effective than currently available agents used to manage these diseases, and may present new options for treatment.

The study will be presented at the ATS 2011 International Conference in Denver.

"We have identified compounds that are more potent than our previously identified set of compounds, paving the way for development of bronchodilators for treating asthma and COPD," said study author Kathryn Robinett, MD, pulmonary and critical care fellow at the University of Maryland School of Medicine. "These compounds represent a new class of bronchodilator that work through an entirely different mechanism than beta-agonists like albuterol, salmeterol and formoterol."

Bitter taste receptors on taste buds of the tongue are thought to have evolved to warn people that they may be ingesting a toxic substance, Dr. Robinett explained. Previous studies revealed these receptors are also present on the smooth muscle surrounding the airways, which constricts in patients with asthma and COPD, reducing the size of the airway and making breathing difficult.

"We had been looking for airway smooth muscle receptors that, when

activated, can relax this muscle for the past five years, and we were excited to find compounds that caused profound relaxation, in both mouse and human airways," she said.

For their study, the researchers examined compounds known to be bitter suggesting they may be effective in relaxing these airway muscles. Once potential compounds were identified, the researchers administered these compounds to mouse airways to examine their effects.

They found that bitter compounds were at least as effective as beta-agonists in relaxing smooth airway muscle. Relaxation of active tension in these muscles in mice approached 100 percent for most compounds, compared to 30 percent for the beta-agonist isoproterenol. In a more limited number of studies in human airways, they continue to find bitter compounds to be somewhat more effective than beta-agonists. More importantly, they appear to work in different ways inside the cell, so the two classes of drugs can work together to treat moderate to severe obstructive lung disease.

"These findings continue to support data that bitter taste receptor agonists could be the next major class of therapeutics in treating asthma and chronic obstructive pulmonary disease," Dr. Robinett said.

Obstructive lung disease, including asthma and COPD, continues to be a significant source of morbidity and mortality affecting 300 million people worldwide.

"Unfortunately, despite widespread use of inhaled corticosteroids and long acting beta-agonists, and environmental controls, as many as one-half of people in the U.S. alone have inadequate control of asthma," Dr. Robinett said. "Bitter taste receptor agonists may add to our armamentarium of treatment options."

Despite their impressive efficacy, the researchers found many of the compounds activate only one or two of the six main bitter taste receptors on airway smooth muscle, meaning that they may not taste very bitter on the tongue, which has 25 bitter receptors.

"We continue to be amazed at the breadth of substances that activate these receptors," Dr. Robinett said. "The plant world is packed with agents that can be effective therapeutics at these targets, or can provide us with the 'molecular backbone' to synthesize compounds that would be better drugs."

Dr. Robinett said this study is just the first step in a much larger task: identifying the compounds which offer optimal results for COPD and asthmatic patients.

"There are over 10,000 compounds that are known to be bitter taste receptor agonists," she said. "These come from plants, including medicinal herbs and food additives, or are synthetic agents that are used for entirely different medical reasons (such as chloroquine for treating malaria). So, we have not only uncovered a previously unrecognized way to open the airways in asthma and COPD, but we have many compounds to consider either 'as they are,' or as backbones for synthesizing a new agent.

"Our challenge, then," Dr. Robinett continued, "is to find safe agents that are not so bitter-tasting as to make them unpalatable, and yet are able to affect the degree of relaxation of airway smooth-muscle that we have found in experimental models.

"Our immediate focus is to gain a better understanding of second messenger pathways and desensitization of bitter taste receptors, to continue to search for more agonists, and to carry out toxicology studies on selected compounds," Dr. Robinett said. "Then, with a set of our 'best

compounds' we will begin the process for Phase 1 clinical trials."

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