New research may explain why obese people have higher rates of asthma

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A new study led by Columbia University Medical Center (CUMC) researchers has found that leptin, a hormone that plays a key role in energy metabolism, fertility, and bone mass, also regulates airway diameter. The findings could explain why obese people are prone to asthma and suggest that body weight–associated asthma may be relieved with medications that inhibit signaling through the parasympathetic nervous system, which mediates leptin function. The study, conducted in mice, was published in the online edition of the journal *Cell Metabolism*.

"Our study started with the clinical observation that both obesity and anorexia can lead to asthma," said Gerard Karsenty MD, PhD, professor and chair of genetics and development and professor of medicine at CUMC, and lead author of the study. "This led us to suspect that there must be a signal coming from fat cells that somehow affects the lungs —directly or indirectly." The most likely candidate was leptin, a protein made by fat cells that circulates in the bloodstream and travels to the brain.

Extensive evidence shows that obesity can cause narrowing of the airways (bronchoconstriction). When obesity develops in people with asthma, it exacerbates the breathing disorder and hampers its treatment through mechanisms that are poorly understood. The current study was designed to elucidate the genetic and molecular bases of the relationships among obesity, airway diameter, and lung function.

Through mouse studies, the researchers showed that abnormally low or

high body weight and fat mass results in bronchoconstriction and diminished lung function. Next, they showed that leptin increases airway diameter independently of, and at a lower threshold than, its regulation of appetite.

Leptin affects the airways by decreasing the activity of the parasympathetic nervous system, a branch of the autonomic nervous system not usually associated with leptin. The researchers also showed that regulation of airway diameter occurs regardless of local inflammation in the bronchi.

The researchers conducted two subsequent experiments to determine if these findings might have bearing on asthma therapy. In one, they took obese, asthmatic mice and administered a substance that increases lung inflammation. When they infused leptin in the brain of these mice for four days, "There was no effect on inflammation, but airway diameter and lung functions were normal," said Dr. Karsenty. "This showed that, at least in the mouse, you can cure obesity-related asthma without affecting inflammation." In the second experiment, the researchers treated obese, asthmatic mice with drugs that decrease parasympathetic tone, or rate of neuronal firing. Again, the asthma abated after several days.

"The therapeutic implication is that it may be possible to correct asthma in obese people with drugs that inhibit parasympathetic signaling—and thereby increase leptin-related brain signaling," said Dr. Karsenty. Such drugs are already available. One is methacholine (Provocholine®, manufactured by Methapharm Inc.), which is used primarily to diagnose bronchial hyperreactivity, the hallmark of asthma. Clinical trials are needed before this or a more active and selective drug can be recommended for the treatment of body weight–associated asthma, Dr. Karsenty added.

The title of the paper is "Inhibition of leptin regulation parasympathetic signaling as a cause of extreme body weight associated asthma." The other contributors are Emilio Arteaga-Solis, Tiffany Zee, Charles W. Emala (CUMC); and Charles Vinson, and Jürgen Wess (NIH).

Provided by Columbia University Medical Center