Discovery may lead to powerful new therapy for asthma

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University of Texas Medical Branch at Galveston researchers have found that a single enzyme is apparently critical to most allergen-provoked asthma attacks — and that activity of the enzyme, known as aldose reductase, can be significantly reduced by compounds that have already undergone clinical trials as treatments for complications of diabetes.

The discovery, made in experiments conducted with mice and in human cell cultures, opens the way to human tests of a powerful new treatment for asthma, which today afflicts more than 20 million Americans. Such a development would provide a badly needed alternative to current asthma therapy, which primarily depends on hard-to-calibrate inhaled doses of corticosteroids and bronchodilators, which have a number of side effects.

"Oral administration of aldose reductase inhibitors works effectively in experimental animals," said UTMB professor Satish Srivastava, senior author of a paper on the discovery appearing in the Aug. 6 issue of the journal PLoS One. "If these drugs work as well in humans as they do in animals you could administer them either orally or in a single puff from an inhaler and get long-lasting results."

Srivastava and his colleagues (postdoctoral fellows Umesh Yadav and Leopoldo Aguilera-Aguirre, associate professor Kota Venkata Ramana, professor Istvan Boldogh and LSU Health Sciences Center assistant professor Hamid Boulares) focused on aldose reductase inhibition as a possible asthma therapy after establishing an essential role for the

enzyme in other diseases also characterized by inflammation. In disorders such as colon cancer, atherosclerosis, sepsis and uveitis, the Srivastava team has found, cells are hit by a sudden overload of reactive oxygen species (varieties of oxygen and oxygen compounds that are especially eager to react with other molecules). The result is a chain of biochemical reactions that leads the cells' genetic machinery to crank out a barrage of inflammatory signaling proteins. These summon immune system cells and generate even more reactive oxygen species, producing a vicious cycle of ever-increasing inflammation.

Aldose reductase plays an essential part in the activation of the cellular machinery that produces inflammatory proteins in these diseases, the Srivastava group discovered. "We found that if you block aldose reductase, you block the inflammation," Srivastava said. "Now, asthma, a chronic disease of inflammation is augmented by reactive oxygen species. So we thought, why not find out if aldose reductase inhibition also has an effect on asthma?"

In an initial series of in vitro experiments, the researchers applied ragweed pollen extract (ragweed pollen is notorious for provoking the allergic reactions that lead to allergies and asthmatic airway inflammation) to cultures of human airway epithelial cells —the cells that line the network of air passages within the lungs. Some of the cultures had been pretreated with an aldose reductase inhibitor, while others had not.

The untreated cells responded in much the same way airway cells do in an asthma attack, with an increased rate of apoptosis (cell suicide), a jump in the levels of reactive oxygen species, the activation of key "transcription factors" that kick-start the production of inflammatory proteins and the large-scale generation of a whole host of molecules associated with inflammation. Cells treated with aldose reductase inhibitors, by contrast, had a much lower rate of apoptosis, reduced

levels of reactive oxygen species, far smaller increases in critical transcription factors and substantially lower increases in inflammatory signaling molecules.

In collaboration with Boldogh, Srivastava next investigated whether aldose reductase inhibitors could reduce the asthma-like symptoms of mice exposed to ragweed extract, a well-established clinical model mimicking the allergic airway inflammation that commonly leads to asthma in humans. When untreated mice inhaled ragweed extract, their lungs suffered an influx of eosinophils (inflammation-inducing white blood cells), a jump in inflammatory signaling molecules, a buildup of mucin (a protein component of mucus) and an increase in airway hyper-reactivity (the tendency of air passages to suddenly constrict under stress). Mice fed a dose of aldose reductase inhibitor before inhaling ragweed extract, however, showed dramatically reduced levels of these components of the asthmatic response.

"Our hypothesis performed exactly as expected, with the experiments showing that aldose reductase is an essential enzyme in the transduction pathways that cause the transcription of the cytokines and chemokines known to act in asthma pathogenesis," Srivastava said. "They attract eosinophils and cause inflammation and mucin production in the airway."

The next step, Srivastava said, will be clinical trials to determine whether aldose reductase inhibitors can relieve asthma in humans. The researcher expressed optimism about their potential outcome of the trials, as well as gratitude to the UTMB National Institute of Environmental Health Sciences Center and the sole supporter of his asthma work, the American Asthma Foundation, which last year awarded him a three-year $750,000 research grant.

"Really, a lot of the credit for this belongs to the AAF," Srivastava said.

"Our primary interest is in cancer and the secondary complications of diabetes, but we were attracted to asthma pathogenesis because the AAF invited me to apply for a grant. I think they're going to be happy with the results."

Source: University of Texas Medical Branch at Galveston (news : web)