Discovery of a "neurotransmitter" system in airway epithelial cells could mean asthma patients will breathe easier

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Sunnybrook researchers (in collaboration with scientists at University of Toronto, University of Manitoba and McMaster University) have found a surprising connection between a major "neurotransmitter" (GABA) and the overproduction of mucus in the airway's epithelial cells. Mucus overproduction is a common symptom of asthma, and this discovery could mean new and improved treatments for asthmatic patients in the future.

The study entitled, "A GABAergic system in airway epithelium is essential for mucus overproduction in asthma" published Sunday in Nature Medicine online, found that the subtype A GABA receptor (GABAAR) and the GABA synthetic enzyme glutamic acid decarboloxylase are expressed in the airway's epithelial cells, form a GABA signaling system. This signaling system becomes activated during an asthmatic reaction, causing mucus overproduction in the airway. This was observed first in a mouse model, and also proved to be the case in airway biopsies of human subjects with asthma. Researchers found that when asthmatic mice inhaled substances that block the GABA signaling system, the airway's mucus production is greatly reduced.

Dr. Wei-Yang Lu, principal investigator of the study, explains why this discovery is exciting for his research team, "This is a significant finding as there is currently no asthma treatment that addresses the overproduction of mucus. Asthmatic attacks produce mucus over-secretion from airway epithelial cells and airway smooth muscle contraction, resulting in airway narrowing and hence shortness of breath. The inhalation of adrenaline using a "puffer" induces airway smooth muscle relaxation, but does little to impede mucus production. Given that severe asthma attacks are more related to the overproduction of mucus, reducing mucus production by blocking the GABA signaling system could be a better treatment for many asthmatic patients."

Allergic asthma is initiated by immune response; meaning it begins in response to inhaled foreign substances. Immune cells in the lung release multiple cytokines, which in turn stimulate reactions in airway epithelial cells and smooth muscle cells. The research team, which included Dr. Lu's lab at Sunnybrook, Dr. Xi Yang's lab at University of Manitoba and Dr. Mark Inman's lab at McMaster University, found that the cytokine interleukens-13 in particular plays a critical role in activating the GABA signaling in the airway epithelial cells during an asthmatic reaction.

Dr. Lu emphasizes again that this airway epithelial GABA system is not associated with airway inflammation, nor with airway smooth muscle contraction in asthma, as these symptoms were not stopped by blocking GABAARs. This makes this GABA signaling system a specific target for management of mucus overproduction in asthmatic attacks. Clinical trials will be the next phase required to determine the exact effect of GABA antagonists in humans with asthma.

These findings have implications for other areas of medicine as well, including anaesthesia. The front line cells facing inhaling anaesthetics are lung epithelial cells, which makes the finding of GABAARs in these cells important as general anaesthetics frequently target GABAARs to take effect. On-going studies in Dr. Lu's laboratory indicate that inhaling anaesthetics change GABAAR activity in lung epithelial cells, thus potentially affecting pulmonary function. What this potential affect is in the short and long-term requires further research. Funding for the study was supplied by the Canadian Institute for Health Research (CIHR.)

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