Anti-inflammatory drugs may strengthen airway immunity to fight infections, study suggests

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Toxins from mold found growing on nuts or corn can weaken the airways' self-clearing mechanisms and immunity, opening the door for respiratory diseases. Credit: Perelman School of Medicine at the University of Pennsylvania

Toxins from mold found growing on nuts or corn can weaken the airways' self-clearing mechanisms and immunity, opening the door for respiratory diseases and exacerbating existing ones, suggests a study in *Scientific Reports* published this month from otolaryngology researchers at the Perelman School of Medicine at the University of Pennsylvania.

Poisonous and cancer-causing, aflatoxins are a type of mycotoxins produced by certain fungi (Aspergillus flavus, for example) growing on and in certain foods. Overall, 25 percent of the world's food crops are contaminated with these molds, though exposure often occurs via contaminated dust inhaled during food processing. They are known to cause allergic fungal rhinosinusitis and bronchopulmonary aspergillosis, two infections that can be treated with antifungal medications and surgery, if needed. However, the downstream effects of aflatoxins on the airway passage is less studied and understood.

In laboratory imaging experiments with human upper airway cells, researchers showed that acute exposure to aflatoxins slowed down and impaired key defense mechanisms in the airways, including mucosal ciliary clearance (MCC) and ciliary beat frequency (CBF). Cilia are tiny, hair-like structures that line the airways and clean out dust and dirt.

The results suggest that aflatoxins enhance the pathogenicity of the fungi and possibly other co-infecting pathogens, such as bacteria.

"With these defenses impaired, it may create a window of opportunity for the infection, and potentially a domino effect," said lead author Robert J. Lee, PhD an assistant professor in the departments of Otorhinolaryngology: Head and Neck Surgery and Physiology at Penn.

Added senior author Noam A. Cohen, MD, PhD, an associate professor of Otorhinolaryngology at Penn: "Patients may become more susceptible to upper respiratory infections and chronic rhinosinusitis (CRS) that can

'seed' lower respiratory infections, especially in those with a compromised immune system. It can also exacerbate the more severe lung diseases, such as cystic fibrosis or chronic obstructive pulmonary disease."

In immunocompromised individuals (chemotherapy patients, for example) or poorly controlled diabetics, upper airway Aspergillus infections can invade the mucosa and underlying tissue and become lethal, so it is particularly critical to understand its interactions with the airway epithelium. A better understanding of the complex pathogenesis of the fungal infection could lead to novel therapies and improve outcomes for these airway diseases, the authors wrote.

The Penn researchers found that the fungal toxins activate protein kinase C (PKC), which decreases ciliary beat frequency and thus decreases MCC. That increased kinase activity presents a potential treatment opportunity, they said.

PKC inhibitors are anti-inflammatory drugs that have been shown to be efficacious in cardiovascular disease and some mental health disorders. In the study, the team found that CBF reductions were blocked by the PKC inhibitors Gö6983 and calphostin C, suggesting that drugs with similar activity could potentially be used to treat the fungal infection and prevent further co-infections.

Importantly, the use of such drugs to treat the infections may lessen the need for patients—as well as livestock and pets—to be on antibiotics, which are often necessary to treat the ensuing bacterial infections that can occur after the airways have been contaminated. A significant amount of aflatoxin contamination occurs in grain-based livestock and pet foods, as well.

What's more, upper respiratory infections often result in CRS, which

causes $8 billion in yearly direct healthcare costs in the United States alone and accounts for about 20 percent of adult antibiotic prescriptions, making it a driver of antibiotic resistance. Antibiotic use in animals is another driver for the emergence of resistant pathogenic microorganisms.

"PKC inhibitors may decrease fungal respiratory disease and ultimately help alleviate some of those consequences," Cohen said.

The effects observed in this study are in response to acute aflatoxin exposure. "Longer-term studies of the effects of aflatoxins will help to shed light on situations of chronic exposure and effects on airways," they wrote.

More information: Robert J. Lee et al. Fungal Aflatoxins Reduce Respiratory Mucosal Ciliary Function, *Scientific Reports* (2016). DOI: 10.1038/srep33221

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