Study sheds light on late phase of asthma attacks

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New research led by scientists from Imperial College London explains why around half of people with asthma experience a 'late phase' of symptoms several hours after exposure to allergens. The findings, published in the journal *Thorax*, could lead to better treatments for the disease.

An estimated 300 million people suffer from asthma, and the prevalence is rising. Symptoms are commonly triggered by allergens in the environment, such as pollen and dust mites. These stimuli can cause the airways to tighten within minutes, causing breathing difficulties which range from mild to severe. Many sufferers also experience a 'late asthmatic response' three to eight hours after exposure to allergens, causing breathing difficulties which can last up to 24 hours.

In the early asthmatic response, the allergen is recognised by mast cells, which release chemical signals that cause the airways to narrow. In contrast, the mechanism behind the late phase has remained unclear.

In research on mice and rats, the Imperial team have now found evidence that the late asthmatic response happens because the allergen triggers sensory nerves in the airways. These nerves activate reflexes which trigger other nerves that release the neurotransmitter acetylcholine , which causes the airways to narrow. If the findings translate to humans, it would mean that drugs that block acetylcholine – called anticholinergics – could be used to treat asthma patients that experience late phase responses following exposure to allergens.

Steroids are the main treatments for asthma prescribed now, but they are not effective for all patients. A recent clinical trial involving 210 asthma patients found that the anticholinergic drug tiotropium improved symptoms when added to a steroid inhaler, but the reason for this was unexplained.

"Many asthmatics have symptoms at night after exposure to allergens during the day, but until now we haven't understood how this late response is brought about," said Professor Maria Belvisi, from the National Heart and Lung Institute at Imperial College London, who led the research. "Our study in animals suggests that anticholinergic drugs might help to alleviate these symptoms, and this is supported by the recent clinical data. We are seeking funding to see if these findings are reproduced in proof of concept clinical studies in asthmatics."

The researchers hypothesised that sensory nerves were involved after observing that anaesthesia prevented the late asthmatic response in mice and rats. They succeeded in blocking the late asthmatic response using drugs that block different aspects of sensory nerve cell function, adding further evidence for this idea.

After establishing that sensory nerves detect the allergen, the researchers tested the effect of tiotropium, an anticholinergic drug that is used to treat chronic obstructive pulmonary disease. Tiotropium blocks the receptor for acetylcholine, which is released by nerves in the parasympathetic nervous system. Tiotropium also blocked the late asthmatic response, suggesting that parasympathetic nerves cause the airways to constrict.

The study was funded by the Medical Research Council (MRC).
Professor Stephen Holgate, MRC funding board chair and an expert on asthma, said: "Unravelling the complex biology of asthma is vitally important, as it is an extremely dangerous condition which exerts

lifelong damaging effects. The Medical Research Council is committed to research that opens doors to improving disease resilience, particularly in conditions which attack our body over the long-term. Studies like this are making really important progress and whilst we must always be cautious when taking findings from rodents into humans, these are very interesting and potentially important results."

More information: K. Raemdonck et al. 'A role for sensory nerves in the late asthmatic response.' *Thorax*, 2011. doi:10.1136/thoraxjnl-2011-200365

Provided by Imperial College London