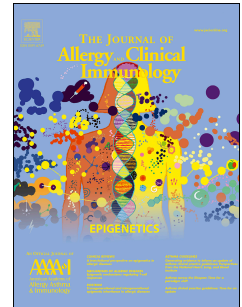


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Why do asthmatics cough? New Insights into Cough in Allergic Asthma

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Cough is a common and troublesome symptom in patients with asthma, in whom the interactions among airway hyperactivity, bronchospasm, airway wall inflammation, and inevitable environmental exposures (allergens, viruses, and irritants) make effective management of cough a clinical challenge. How then do we understand the etiology of cough, and how can we use that understanding to improve care of patients with asthma? The study by Satia *et al*¹ in this issue of the Journal suggests that airway inflammation from allergen exposure and consequent bronchospasm are associated with increased sensitivity of the capsaicin-induced cough reflex. The key findings of this work were that capsaicin-induced cough was increased following allergen challenge compared with saline challenge, and was independently associated both with airway eosinophilia and airway obstruction. Why capsaicin challenge, and how does that relate to cough in clinical practice? Capsaicin-induced cough is an established model that has provided important insights into the mechanisms of cough in human subjects by exploring the susceptibility of the patient to cough. Although the exact physiologic and molecular mechanisms are not fully elucidated, there is growing evidence that both cellular and humoral pathways are involved, specifically eosinophils, eosinophil granule proteins, inflammatory cytokines, and TRP (transient receptor potential) receptor family²⁻⁷.

The effects of capsaicin, methacholine and inhaled allergen have been subjects of research for decades. Collectively, there is evidence that cough sensitivity in asthma is increased in relation to bronchospasm⁶, airway neuronal dysfunction⁷, airway inflammation, and allergen exposure¹. Capsaicin-induced cough in humans is mediated by the TRPV1 (TRP cation channel, subfamily V, or the vanilloid) receptor expressed on afferent non-myelinated C fibers, which largely originate in the jugular ganglia⁴⁻⁵. Non-myelinated C fibers have intrapulmonary terminations throughout the airways and lungs as well as extra pulmonary terminations. A_δ fibers originate in the jugular basal and nodose ganglia of the vagus and have few intra pulmonary terminations, and may mediate cough from more proximal airways^{4,8}. In addition, C-fibers and A_δ fibers are activated by ATP (adenosine triphosphate), via P2X, P2Y receptors and P2X3-containing trimers⁹. The mechanism by which capsaicin induces bronchospasm (*versus* cough) in humans is unknown. In contrast, methacholine stimulates muscarinic (M3) postganglionic parasympathetic receptors, which results in smooth muscle contraction and mucus secretion. Allergen exposure can directly activate other receptors (TRPA1, TRP cation channel, subfamily A, member 1) associated with cough, and in sensitized subjects allergen exposure induces the release of inflammatory mediators (interleukins, prostaglandins, histamine³) and recruitment of inflammatory cells that further heighten cough responses. Further, allergen exposure in sensitized individuals increases the expression of TRPV1 receptors on airway nerves. Importantly, activated eosinophils infiltrate airway nerves, and release of eosinophil granule proteins accentuates neural signaling, and can potentiate cough². This understanding informs development of targeted therapies directed towards the underlying pathogenesis of cough (Fig 1A).

The current study utilized a strong experimental design that mitigates the relatively small number of subjects. The authors demonstrated that increases in capsaicin-induced cough were correlated with airflow obstruction in the early asthmatic response, and with both airflow obstruction and sputum eosinophilia in the inflammatory late asthmatic response. These data argue that both airway caliber (bronchospasm) and the development of airway inflammation (eosinophilia) are independently important in the pathogenesis of cough.

Several technical limitations should be recognized. The locale of capsaicin deposition before and after the allergen challenge is not known. A change in airway caliber theoretically could alter airflow dynamics, and change the distribution of capsaicin particles to interact with TRPV1 receptors at a more proximal or more distal location in the airway, which might produce a different profile of cough. A ventilation radionuclide study may be necessary to evaluate this possibility. Sputum eosinophilia is an indirect marker of airway wall inflammation and provides little information on the activation state of the recovered eosinophils. Eosinophils play an important role in inflammation in asthmatic patients, but other cells may also be important. Therefore, airway biopsies would have been helpful to understand the type of inflammation and could also have assessed the level of expression of TRPV1 receptors.

Suppression of airway inflammation is essential in the management of persistent asthma. Currently, targeted therapies to control eosinophilic airway inflammation (both steroids and monoclonal antibodies) have proven beneficial. Knowing that cough in asthma patients can also be related to sensitization of cough reflex has led to the suggestion that blocking some of its components (TRP and P2X3 receptors) might help in the management of this troublesome symptom^{9,10}. Currently, there are no approved therapies that target TRP or P2X3 receptors in humans; the science of antagonism of these receptors is a developing field and drugs are in development^{9,10}. However, effects of these agents on cough in humans is unknown.

What then have we learned from this work and how might it impact clinical medicine? Clinicians have known for decades that allergen exposures that induce worsening of asthma cause cough, bronchoconstriction, hyper-responsiveness, and dyspnea. A consistent finding in existing literature suggests that it is not possible to separate airway constriction from increased cough sensitivity. A variety of models, both inflammogenic and non-inflammogenic, demonstrate the coupling of cough to bronchospasm^{1,6,7}. This finding would argue that a key therapeutic strategy for cough management in asthma is to minimize bronchospasm and maximize FEV1. This study, coupled with others, highlights the importance of controlling airway caliber to mitigate cough. However, the degree of cough sensitivity is also separately associated with airway inflammation, indexed by Satia as sputum eosinophilia. This finding would suggest that cough management in asthma must also include effective anti-inflammatory, and perhaps anti-eosinophil, strategies. This work provides strong scientific rationale for such treatment. Dissecting the pathophysiology of the mechanisms behind cough in patients with asthma can help clinicians and scientists develop use and develop targeted therapies that can individually and in combination better manage symptoms and improve quality of life (Fig 1B).

References

1. Satia I, Watson R, Scime T, Dockry RJ, Sen S, Ford JW, et al. Allergen challenge increases capsaicin-evoked cough responses in patients with allergic asthma. *Journal of Allergy and Clinical Immunology*. 2019 Jan 17.
2. Costello RW, Schofield BH, Kephart GM, Gleich GJ, Jacoby DB, Fryer AD. Localization of eosinophils to airway nerves and effect on neuronal M2 muscarinic receptor function. *American Journal of Physiology-Lung Cellular and Molecular Physiology*. 1997 Jul 1;273(1):L93-103.
3. Birring SS, Parker D, Brightling CE, Bradding P, Wardlaw AJ, Pavord ID. Induced sputum inflammatory mediator concentrations in chronic cough. *American journal of respiratory and critical care medicine*. 2004 Jan 1;169(1):15-9.
4. Brooks SM. Irritant-induced chronic cough: irritant-induced TRPpathy. *Lung*. 2008 Feb 1;186(1):88-93.
5. Groneberg DA, Niimi A, Dinh QT, Cosio B, Hew M, Fischer A, et al. Increased expression of transient receptor potential vanilloid-1 in airway nerves of chronic cough. *American journal of respiratory and critical care medicine*. 2004 Dec 15;170(12):1276-80.
6. Satia I, Badri H, Woodhead M, O'byrne PM, Fowler SJ, Smith JA. The interaction between bronchoconstriction and cough in asthma. *Thorax*. 2017 Dec 1;72(12):1144-6.
7. Satia I, Tsamandouras N, Holt K, Badri H, Woodhead M, Ogunbenro K, et al. Capsaicin-evoked cough responses in asthmatic patients: evidence for airway neuronal dysfunction. *Journal of Allergy and Clinical Immunology*. 2017 Mar 1;139(3):771-9.
8. Muroi Y, Ru F, Chou YL, Carr MJ, Undem BJ, Canning BJ. Selective inhibition of vagal afferent nerve pathways regulating cough using Nav 1.7 shRNA silencing in guinea pig nodose ganglia. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 2013 Apr 10;304(11):R1017-23.
9. Ford A, Undem B. The therapeutic promise of ATP antagonism at P2X3 receptors in respiratory and urological disorders. *Frontiers in cellular neuroscience*. 2013 Dec 19;7:267.
10. Khalid S, Murdoch R, Newlands A, Smart K, Kelsall A, Holt K, et al. Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: a double-blind randomized controlled trial. *Journal of Allergy and Clinical Immunology*. 2014 Jul 1;134(1):56-62.

Figure Legends

Figure 1A. Factors Associated with Cough in Asthma

Figure 1B. How can we implement this knowledge?

