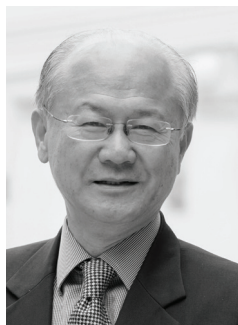


Cough Hypersensitivity Syndrome – A Major Advance in the Understanding of Chronic Cough

An Expert Interview with Kian Fan Chung

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Kian Fan Chung

Kian Fan Chung is Professor of Respiratory Medicine and Head of Experimental Studies Medicine at National Heart & Lung Institute, Imperial College London, and is Consultant Physician at the Royal Brompton & Harefield NHS Trust, London. Professor Chung is active in clinical research into asthma and cough, with the aim of improving detection of respiratory disease and discovering and applying new treatments. He is an international authority on the treatment of chronic airway diseases and has published over 600 medical and scientific articles on many aspects of respiratory diseases and respiratory medicine. He has co-edited several books on lung diseases such as Pharmacology and therapeutics of cough (2008); Pharmacology and therapeutics of airways diseases (2010); and Monograph: Severe difficult-to-treat asthma (2011). He serves on the Editorial Boards of many journals including Lancet Respiratory Medicine, Respirology and European Journal of Pharmacology. He is also a Senior Investigator of the National Institute for Health Research. He has lectured extensively in Europe, North America and Asia.

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Cough is a common complaint that often necessitates a visit to a primary care provider,¹ but typically resolves spontaneously within a few weeks. Chronic cough, which is a cough that has lasted for more than 8 weeks, is a more difficult condition to manage and satisfactory control is not achieved in a substantial number of patients.² It has been suggested that many cases of chronic cough may share a common mechanism: that of a hypersensitive cough response.³ This has led to the definition of a new disease entity: cough hypersensitivity syndrome (CHS).⁴⁻⁶ In an expert interview, Professor Kian Fan Chung of the National Heart & Lung Institute, Imperial College and the Royal Brompton & Harefield NHS Trust, London, UK, discusses CHS and the recent advances in our understanding of this condition that is leading to the development of novel treatment approaches.

Q. What is the difference between chronic cough and cough hypersensitivity syndrome?

Chronic cough is a clinical condition that is defined as cough lasting for at least 8 weeks.² This definition is used to enable clinicians to trigger a series of steps to diagnose any underlying conditions that may be causing the cough, for example a chest X-ray to exclude lung cancer. The patient is then managed according to any associated conditions found according to the set of guidelines set by respiratory societies including the European Respiratory Society (ERS). CHS was defined a few years ago by the ERS as a condition in which the cough is caused by stimuli that don't usually cause cough, or a hypersensitivity to stimuli that are known to be tussive, e.g. citric acid or capsaicin.⁵ While this hypersensitive mechanism has been imputed initially in patients with chronic cough where no cause of the cough has been found, there is now evidence that even in patients with chronic cough associated with conditions such as asthma, chronic obstructive pulmonary disease, pulmonary fibrosis or gastroesophageal reflux disease, this mechanism is underlying the chronic cough. So, patients with CHS may have hypersensitivity to stimuli that do not usually induce coughing e.g. talking, laughing, going outside in cold weather or smelling perfume. Other common complaints are a sensation of having something stuck or irritating in the throat, and difficulty breathing such as a feeling that there is a blockage at the level of the throat and the patient can't get air into the lung. While we don't yet have all the evidence, I believe that most patients presenting with a chronic cough have CHS.

Q. What are the major challenges in the diagnosis and treatment of cough hypersensitivity syndrome?

The diagnosis is not challenging and can be determined, to a large extent, by asking questions about what induces the cough and whether the cough is sensitive to simple tests, including measuring

the cough response to inhaling citric acid or capsaicin. Patients with CHS respond to much lower concentrations of these chemicals than those without CHS. However, we need to find better tests of CHS.

The treatment of CHS, however, remains a challenge – so far there is a lack of good treatments for controlling cough in CHS because we don't understand entirely how this hypersensitivity occurs and the pathways that lead to its cause.

Q. How do you detect cough hypersensitivity syndrome in patients with underlying diseases such as asthma?

I believe that CHS can underlie the chronic cough accompanying many chronic pulmonary inflammatory conditions such as asthma. Chronic cough may persist in patients with asthma whose condition is otherwise well controlled by asthma medications, in this case it is likely that the cough is underlined by CHS. One could assess cough hypersensitivity by measuring the response to citric acid or capsaicin, which are tussive agents, but these tests are not widely used, only in specialised cough centres.

Q. What is the role of adenosine triphosphate in cough sensitisation?

Until recently, we knew little about the role of adenosine triphosphate (ATP). A study in Manchester investigated a compound that blocks the P2X₃ receptor – an ATP binding receptor. This drug was successful in

suppressing cough in patients with idiopathic chronic cough, particularly in those with a high cough rate measured on a cough monitor,⁷ indicating that ATP may be important in cough sensitisation. This also complements previous information that the ATP/P2X₃ axis may be important in bladder overreactivity or chronic visceral pain.⁸ The role of ATP and the P2X₃ receptor in CHS however needs to be fully elucidated. Cough is induced by stimulation of nerve endings in the upper airway by an external stimulus that sends a signal through the vagus nerves to various brain centres to cause the process of cough. ATP and its P2X₃ receptor may work at any part of this process from the upper airways/lungs to the brain.

Q. What novel pharmacological approaches are in clinical development for cough and cough hypersensitivity syndrome?

This concept of CHS is proving useful in allowing researchers to focus on pathways that could be blocked to reduce cough. A P2X₃ receptor antagonist (MK-7264) has now been developed by Merck⁹ and is currently in phase III studies (NCT03449147, NCT03449134). At least two other companies are also working on P2X₃ receptor antagonists. A neurokinin-1 receptor antagonist is also being targeted and phase II clinical studies are in progress.¹⁰ An agonist of the nicotine receptor will soon be going into an early proof of concept study. This is an area of great promise for novel effective antitussives at the moment and research is progressing very quickly. □

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