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Poster discussion: Summary

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Abstract

At the Fifth International Cough Symposium 16 posters were presented and, as well as discussions at the poster sites, were considered in a formal symposium session. Here they are divided into groups and we summarize the discussions.

Keywords

Cough; Cough sensors; Cough neural pathways; Membrane receptors; Clinical cough

1. Introduction

The posters presented at the Fifth International Cough Symposium deal with a variety of important issues related to both basic and clinical research. They covered a wide array of important topics in cough, ranging from ambulatory measurement of coughing in humans with airways diseases to second messenger pathways contributing to the production of coughing in animal models. Such variety witnesses the viability of cough research and confirms that, despite recent advances in our knowledge of cough mechanisms and clinical manifestations, there remain several questions awaiting further elucidation and additional research efforts. What follows is a summary and commentary on these posters.

2. Basic science of cough

Poster presentations by basic scientists, particularly physiologists and pharmacologists, mainly focussed on cough neurophysiology and pharmacological control. Indeed, the central mechanisms of cough production represent an important, but under-investigated area of research. Farmer et al. (Farmer, DG, Mori, N, Canning, BJ: NMDA receptors and nitric oxide synthase regulate the encoding of cough in guinea pigs) showed that nitric oxide plays a role in the antitussive effects of microinjection of NMDA (N-methyl-D-aspartate, a glutamate receptor agonist) into the region of the medial nucleus of the tractus solitarius. Previous investigations evaluated the respiratory and cough modulatory role of NMDA antagonists microinjected into more caudal areas of the brainstem [1–4]. This is an important finding and sets the stage for further investigations into the neuropharmacology of sensory afferent terminals as well as second-order interneurons in this region of the medulla. These investigators also showed that NMDA receptor ligands micro-injected into this region could alter cough without affecting breathing, highlighting the selectivity of the neural control elements that were affected by the drugs.

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Marchal et al. (Marchal, F, Demoulin, B, Varechova, S, Betin, N, LeBlanc, AL: Cough and expiration reflex dependence on timing within the breathing cycle in anaesthetized rabbits) showed that the timing of brief mechanical stimuli is important in the expression of different types of laryngeal airway defensive behaviours in the rabbit. The reasons why the same stimulus can elicit different airway defensive behaviours are not clearly understood. These findings support the concept that different airway defensive behaviours are produced in a non-random manner. Rather, the expression of the behaviours seems to be influenced by the functional state of brainstem neurones, so that during the expiratory phase of normal breathing the expiration reflex is more easily evoked than cough, whereas the opposite is true during the inspiratory phase. The preferential expression of the expiration reflex during the expiratory phase of normal breathing is supported by the brainstem network for this behaviour as proposed by Shannon and coworkers [5]. The proposed expiration reflex network is composed primarily of neurones whose excitability would be higher in the expiratory period of breathing. Taken together, the findings reinforce the possibility that cough and the expiration reflex are sub-served by distinct neural mechanisms [5].

Three poster communications tackled the issue of the pharmacological control of the cough reflex in animal models. The influence of second messenger systems in the production of cough was investigated by Kamei et al. (Kamei, J, Hayashi, S-S, Takahashi, Y, Miyata, S, Ohsawa, M: Role of cyclin-dependent kinase-5 on capsaicin-induced cough in sensitized mice). Roscovitine, a specific cyclin-dependent kinase (Cdk5) inhibitor, was used to investigate the mechanisms of enhanced coughing in ovalbumin-sensitized mice. The enhanced cough caused by allergic sensitization was inhibited by inhalation of roscovitine. Sensitization induced increased substance P and Cdk5 in the lungs of these animals, consistent with C-fibre stimulation. The role of different sensory afferent populations in the production and type of airway defensive behaviours in this species beg further investigation and this study raises interesting questions in this regard.

Stafford et al. (Stafford, SA, Pethen, SJ, Hampton, SL, Evans, DM, Haigh, RM: Kallikrein inhibitors as potential novel anti-tussive treatments) presented evidence that a selective tissue kallikrein inhibitor (VA999024) inhibits citric acid-induced cough in the awake guinea pig. This drug was effective in animals that apparently had no underlying airway inflammation. A possible interpretation of the results is that citric acid induces the release of kallikreins that in turn contribute to the stimulation of sensory afferents that promote cough. Further work on the potential mechanism of this effect would be important, particularly studies addressing the extent to which this molecule can penetrate the central nervous system and/or has activity at acid-sensitive ion channels. Potentially, kallikrein inhibitors represent an important therapeutic tool in cough where the pro-inflammatory role of bradykinin is likely to be involved [6], such as ACEI-induced cough.

Takahama et al. (Takahama, K, Zhuo, J-R, Soeda, F, Shirasaki, T: Do the paratracheal ganglia (PTG) become targets for drugs inhibiting chronic cough? – studies using single PTG neurons and those with synaptic boutons) investigated the actions of suplatast tosilate, a Th2 cytokine inhibitor, on rat and guinea pig PTG neurons. They found that suplatast inhibited currents induced by nicotine and proposed that this drug suppressed acetylcholine release from postganglionic nerve terminals. We look forward to further studies addressing the conditions in which PTG neurones can influence the production of cough in animal models.

3. Clinical research on cough

The results of studies performed by clinical research groups have also attained important outcomes. It seems particularly worth mentioning the effort by two independent units who

have developed methods for 24 h ambulatory monitoring of cough in humans and have assessed their reliability. There is little doubt that potentially this non-invasive technique is a prerequisite for assessing the effectiveness of new therapies for cough.

One study (Mann, VM, Sheedy, W, Wright, C, Thompson, R, Morice, A: Analysis of ambulatory 24-hour cough recordings from idiopathic chronic cough patients) was performed in patients with idiopathic cough and was aimed at exploring the reproducibility of three consecutive cough frequency assessments separated by a 7-day interval. The results demonstrated reproducibility of the assessments within a considerably long time interval, suggesting that the ambulatory recording system is suitable for studying the clinical features of cough in patients with idiopathic cough.

Another study (Kelshall, A, Decalmer, S, McGuiness, K, Woodcock, A, Smith, J: Gender differences in objective cough frequency in patients presenting with chronic cough) explored a larger group of patients with unexplained chronic cough. The results reinforce the notion of a heightened cough reflex in females and show that age is also significantly correlated with increased cough sensitivity. Both of these studies represent efforts to develop and document important tools to improve our knowledge of spontaneous coughing in various patient groups.

Studies performed by various research groups add significantly to the current knowledge on the epidemiology, clinical features and pharmacological control in humans. Recent data suggest that the circulation of *Bordetella pertussis* (BP) occurs in adolescents and adults and is manifest by prolonged cough illnesses, which most often go unrecognized as pertussis [7]. Nonetheless BP infection as a potential cause of persistent cough has been given little attention in recent guidelines [8,9]. Takeda et al. (Takeda, T, Niimi, A, Matsumoto, H, Ito, I, Yamaguchi, M, Matsuoka, H, Jinnai, M, Otsuka, K, Oguma, T, Nakaji, H, Mishima, N: Incidence and clinical features of persistent cough associated with *Bordetella pertussis* infection) have examined the prevalence of BP infection in patients with subacute and chronic cough, and have attempted to identify the distinguishing clinical features of this clinical form of cough. The major finding was that a high percentage (8–11%) of patients with persistent cough has a BP infection. Since, however, the clinical expression of BP-related cough is non-specific, assessments of immunoglobulin G antibody levels are required for definitive diagnosis.

The study by Varechova et al. (Varechova, S, Plevkova, J, Javorkova, N, Martinek, J, Tatar, M, Hanacek, J: Cough reflex sensitivity in school-age healthy children: impact of age, sex, pollution and respiratory morbidity on cough parameters), performed in a large number of children with a median age of 13 years, examined the influences exerted by a number of epidemiological, clinical and environmental factors on cough sensitivity, here conveniently assessed in terms of capsaicin cough threshold (C2). The principal result is that cough sensitivity appears to be affected by factors such as age, pubertal status, gender, respiratory morbidity and exposure to environmental pollutants. The findings also suggest that if one wishes to investigate, for instance, the modulation of cough by an antitussive agent, individual levels of cough sensitivity need to be considered in relation to all the other variables examined in the study.

In their study, Takemura et al. (Takemura, M, Niimi, A, Ueda, T, Matsuoka, H, Yamaguchi, M, Jinnai, M, Matsumoto, M, Mishima, N: Antitussive and anti-inflammatory effects of Montelukast in patients with cough variant asthma) examined a large number of patients with cough-variant asthma in order to investigate the mechanisms of the previously established [10] antitussive effect of leukotriene antagonists. The study is impressive for both the importance of the question addressed and the variety of the methodological

approaches used. The results confirm the antitussive properties of the examined drug and, perhaps more importantly, suggest a causal relationship between the reduction in cough sensitivity by Montelukast and the attenuation of eosinophilic inflammation as assessed by sputum cell counts and sputum levels of several inflammatory mediators. Interestingly enough, the reduction in cough sensitivity was not paralleled by a concomitant reduction in methacholine airway hyperresponsiveness, suggesting different underlying mechanisms.

An interesting study performed on both human and animal models of induced cough in Slovakia sheds light on the possibility of cough up-regulation via non-vagal afferent nerves. It has long been known that chronic cough in humans can be caused by disorders involving the nasal airway [8,9]. However, the mechanisms that are responsible for these clinical observations are unknown. Brozmanova et al. (Brozmanova, M, Plevkova, J, Bartos, V, Plank, L, Kollarik, M, Tatar, M: Experimental allergic rhinitis and the cough reactivity) and Plecova et al. (Plevkova, J, Brozmanova, M, Pecova, Varechova, S, Tatar, M: The cough reactivity changes in healthy and allergic subjects induced by intranasal histamine challenge) presented data in humans and animals that nasal afferents can enhance cough, especially when they are stimulated in allergic conditions. These are novel findings and underscore the utility of animal models in the process of understanding mechanisms of coughing in humans. Furthermore, Brozmanova et al. showed that measures of cough sensitivity (C2) routinely used in humans also can be used in animal models. Last, the results also point at the possibility that non-vagal sensory pathways can modulate cough sensitivity.

4. Pathophysiological studies

Pathophysiological studies performed on normal humans or patients with neurological disease provide novel information regarding the mechanics of cough, expiratory muscle force and cough down-regulation by hyperventilation. As yet, relatively few studies have incorporated indices of mechanics into the investigation of cough in the human. Addington et al. (Addington, WR, Stephens, RE, Phelipa, MMD: Intra-abdominal pressures during voluntary and reflex cough) recorded bladder pressures (equivalent to abdominal pressure) during voluntary and irritant-induced cough in awake female subjects. Bladder pressures during voluntary and irritant-induced cough were robust and had “sawtooth-like” fluctuations in pressure suggestive of repetitive expulsive events that were not separated by inspiratory efforts. A novel finding of the study is the recording of higher bladder pressures during reflex cough, suggesting higher expiratory motor output in this condition. Further investigations including electromyographic recordings and cough airflows may be helpful in discerning the motor strategy utilized by these subjects to produce coughing under both conditions.

An emerging area is the investigation of cough impairment in patients with neurological diseases. Pitts et al. (Pitts, TE, Bolser, DC, Sapienza, C: Effects of expiratory muscle strength training (EMST) on cough and swallow in Parkinson’s disease) presented evidence that both cough and swallow are impaired in this patient population and that a 1-month expiratory muscle strength training paradigm can improve objective measures of both behaviours. The extent to which improvement of aerodynamic measures of cough in these subjects can have a clinically beneficial effect in these patients is currently unknown. Long-term studies on a larger cohort with outcome measures would be an important next step in testing the potential benefits of expiratory muscle strength training to this patient population.

Lavorini et al. have investigated the effect of steady-state exercise and voluntary hyperventilation on cough sensitivity and the urge-to-cough (UTC) to inhaled ultrasonically nebulised distilled water (Lavorini, F, Fontana, G, Pantaleo, T, Widdicombe, J: Cough and

respiratory sensation during exercise and isocapnic hyper-ventilation in humans). In both experimental conditions, cough threshold significantly rose, suggesting cough down-regulation by voluntary and exercise-induced hyperventilation. Conversely, the intensity of the UTC (VAS scale) was unaffected by either experimental condition. It may be that convergence of cortical and reflex stimuli on brainstem neural network sub-serving breathing and cough production down-regulates cough sensitivity. The role played by factors such as varied aerosol distribution or mental distraction also needs to be defined. Additional details on this study can be found elsewhere in this volume.

Last, but not least, an interesting anatomical study on laryngeal development in humans investigated the anatomical relationships in the pharyngeal airway that are likely to be important in airway defense. Stephens et al. (Stephens, RE, Bancroft, A, Glaros, AG, Lowe, LH, Addington, WR: Laryngeal descent in human infants: MRI and radiograph anatomical changes from birth to 1 year) showed linear changes in the rate of change in the distance between the uvula and tip of the epiglottis in the first year of life. There are very few studies investigating the anatomical basis of airway defense. Studies such as this one will be important in testing hypotheses regarding the relationship between anatomical changes in the pharyngeal airway during development and the physiology of airway defense.

5. Conclusion

The posters were excellent. They covered a diversity of aspects of cough including pharmacological and neurological mechanisms, and cough in the clinic. They pointed to the future and should stimulate much research. The presenters deserve to be congratulated.

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